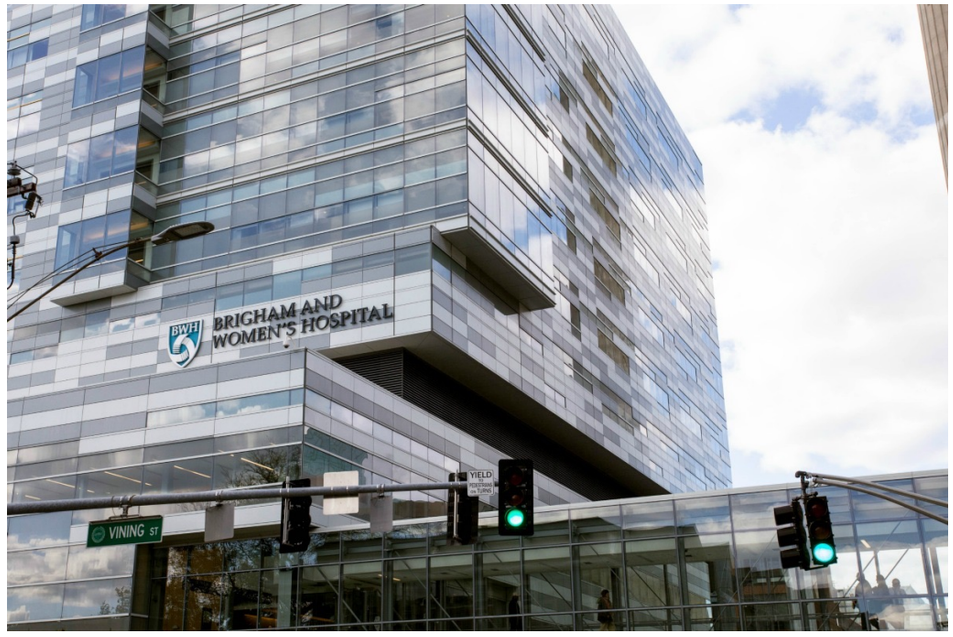

Cystic Fibrosis

In the Era of Highly Effective Modulators

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Adult Director, Therapeutic Development Network, Adult CF Program
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Disclosures

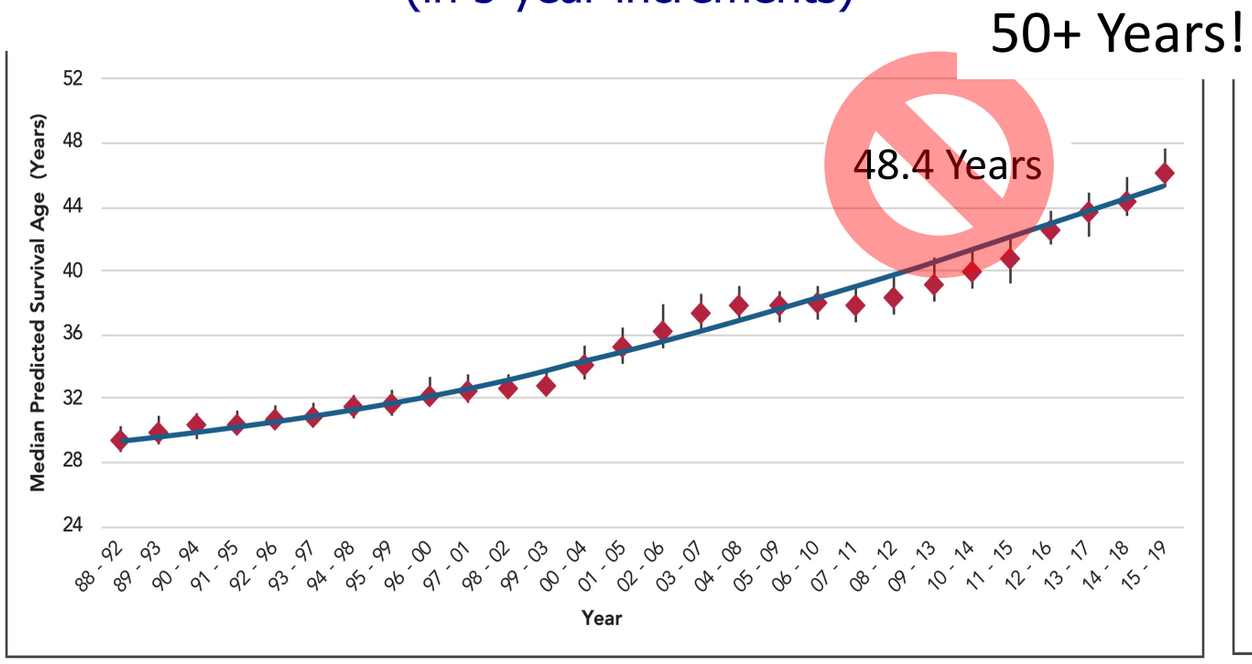
- Cystic Fibrosis Foundation Therapeutic Development Network
- Adult CF Program Principal Investigator
- North American Lead Principal Investigator
    - Vertex VX121-101
    - Eloxx-012

Outline

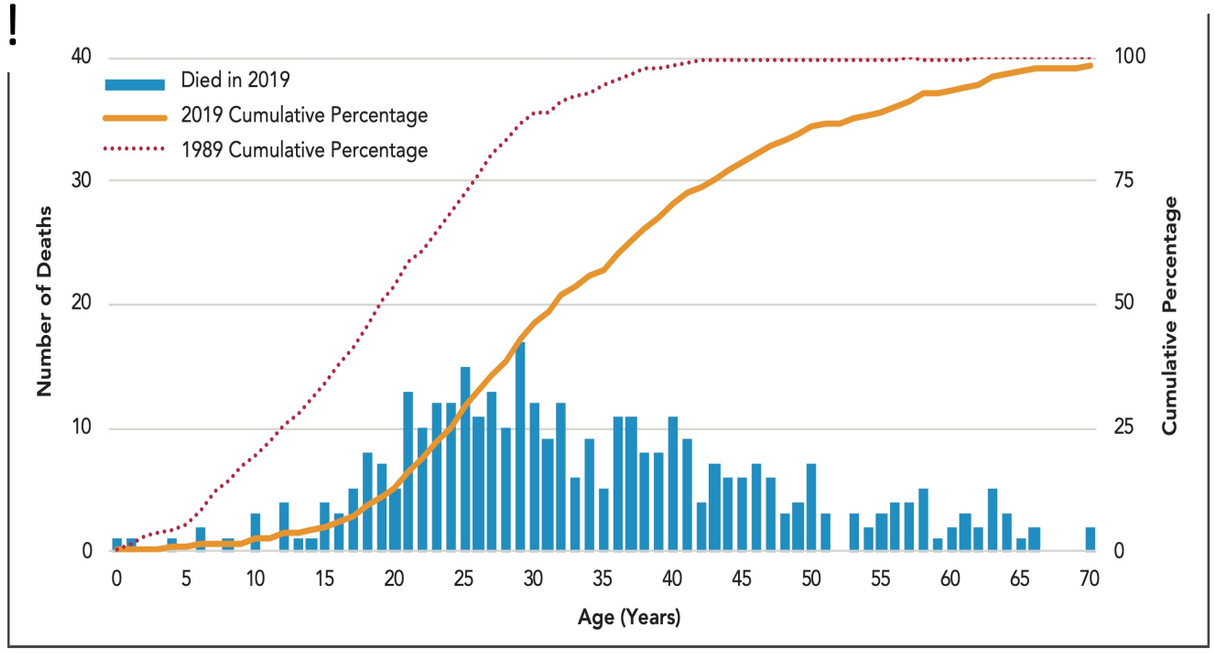
- Introduction to CF and Brief Overview
- Patient Case: 62 year old presenting with bronchiectasis and recurrent exacerbations
- CF Pathophysiology
- Diagnosis and Outpatient Management
- CFTR Modulators and Future
- Conclusion and Questions

Improving Survival

Median Predicted Survival Age, 1988-2019
(in 5 year increments)

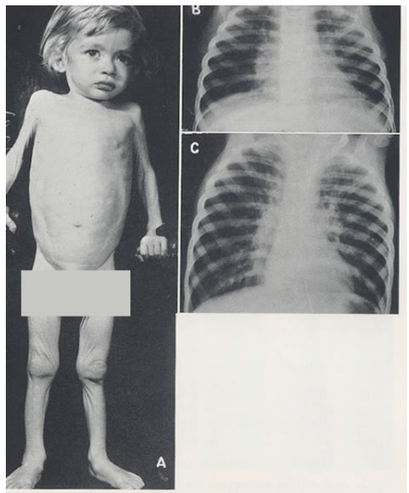


Median Age of Death - 2019



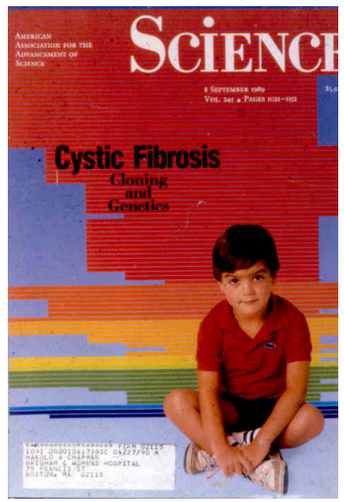
373 deaths reported, median age at death 32.4 years

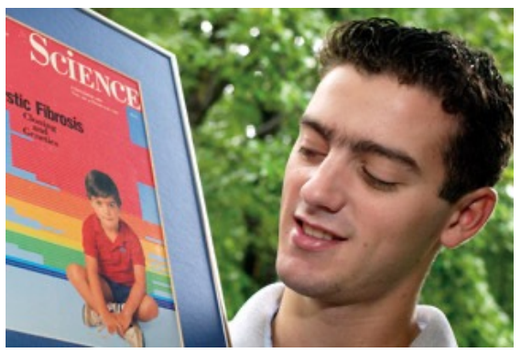
A Story of Progress



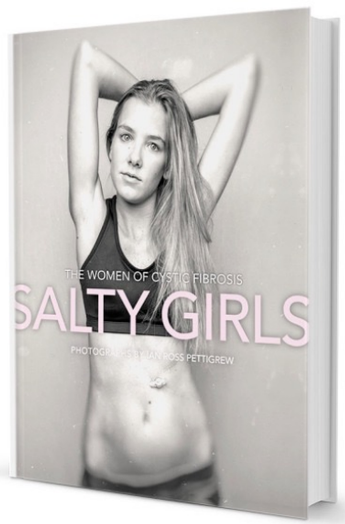
igure 7. A. Patient with Cystic Fibrosis of the Pancreas at two years, ve months. B. Lungs at one year, two months. C. Lungs at two years, ve months. When infection becomes established in the viscid secretion the bronchioles at an early age, and persists, the lungs show progres- ve development of peribronchial infiltration and emphysema. The atritional state deteriorates with advance of the infection. (Repro- uced from Plate V, May, C. D. and Lowe, C. U., Fibrosis of the ancreas in Infants and Children, *J. Pediat., 34*:663 (1949) with per- mission of C. V. Mosby, St. Louis.)

1950





1989



2015

2020

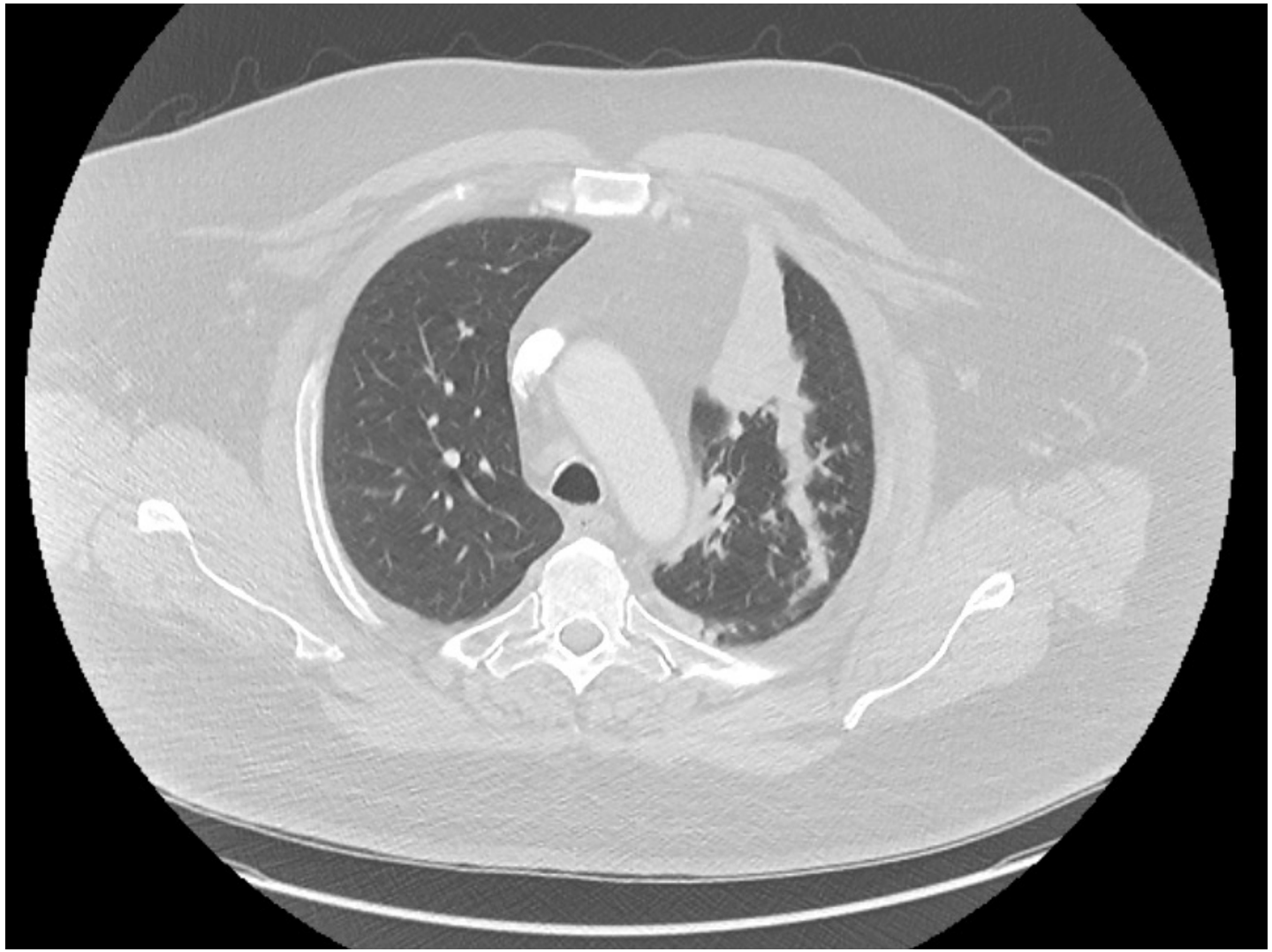
Patient Case

General information	
Age at diagnosis:	--
Current age:	62 years
Sex (M/F):	M
Genotype:	--
Sweat chloride:	--
Lung function:	71% (initial visit)
Medical background (e.g. exacerbations/infection history):	
Pneumonia and recurrent bronchitis since age 14 (yearly) Exacerbations increased to 3-4x/year and chronic cough **Chest CT in 2016 with diffuse nodular opacities and bronchiectasis** **TB testing negative**	

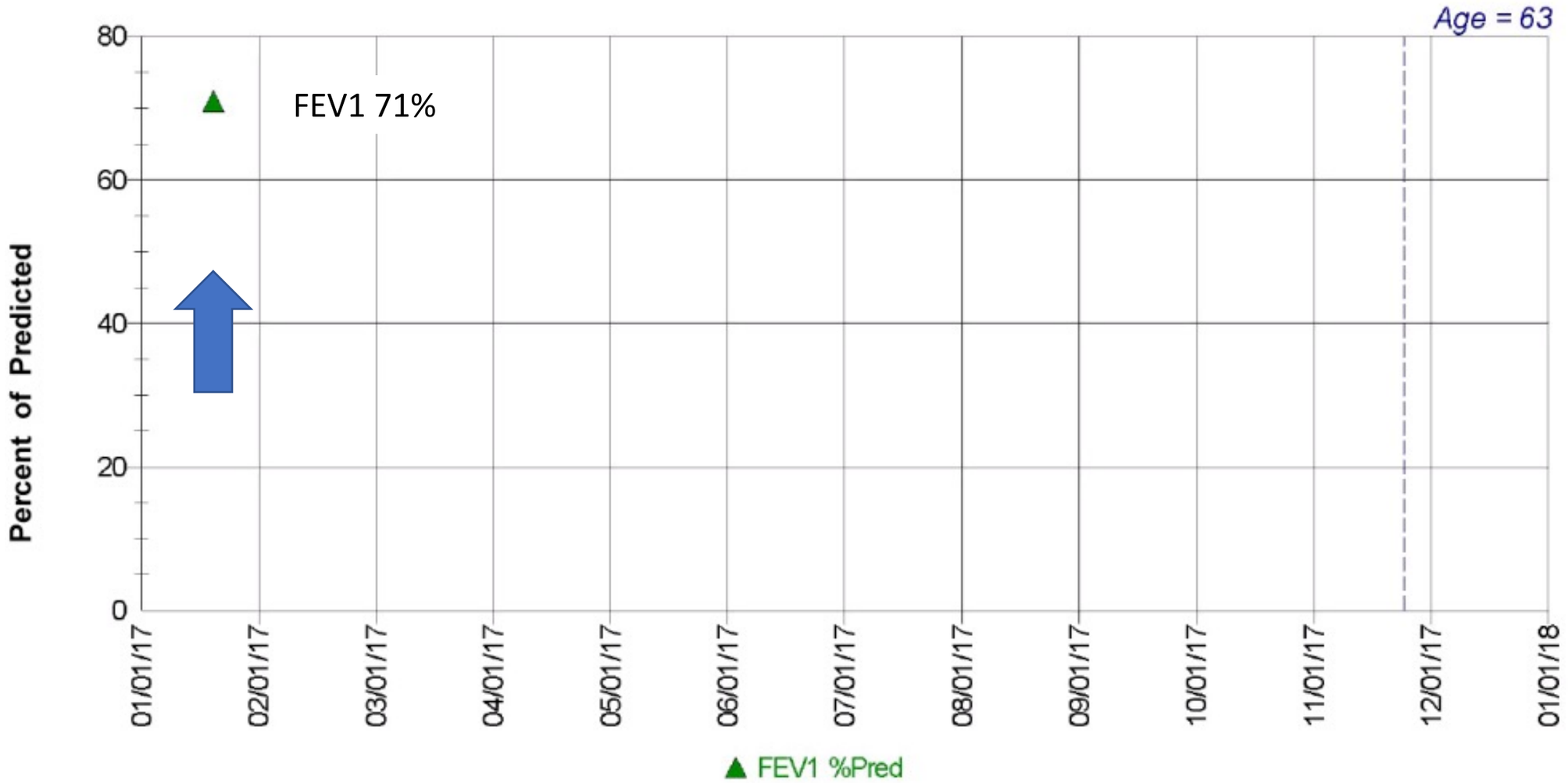
Comorbidities:
Chronic Cough, Recurrent Bronchitis, Obstructive Sleep Apnea, Hypercholesterolemia, Hypertension, GERD, Prostate Ca s/p prostatectomy, Morbid obesity
Lifestyle/circumstance:
Decreased activity, desk job
CFTR Treatment:
Other
Never smoked No Children Family History of Colon cancer

CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

Patient Case



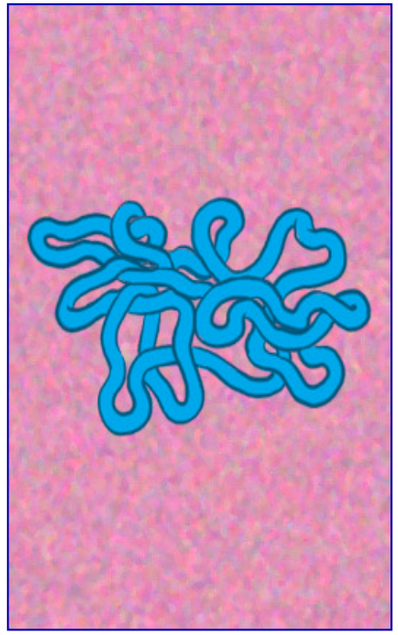
Patient Case



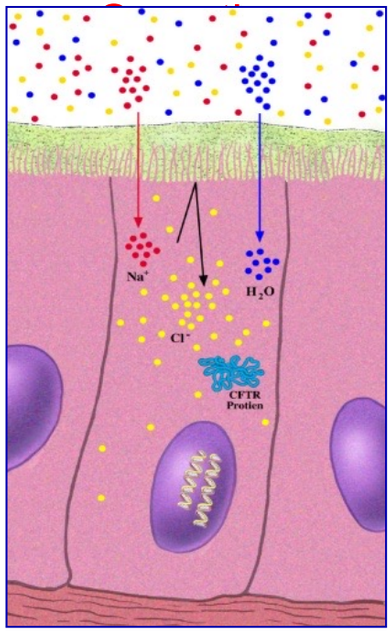
CF Pathophysiology

Abnormal Gene

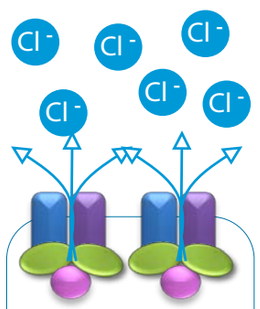
Abnormal Protein



Altered Ion Transport (Cl^- and $HC0^-_3$) & Abnormal Mucus



5 (or 6) Classes of CFTR Mutations



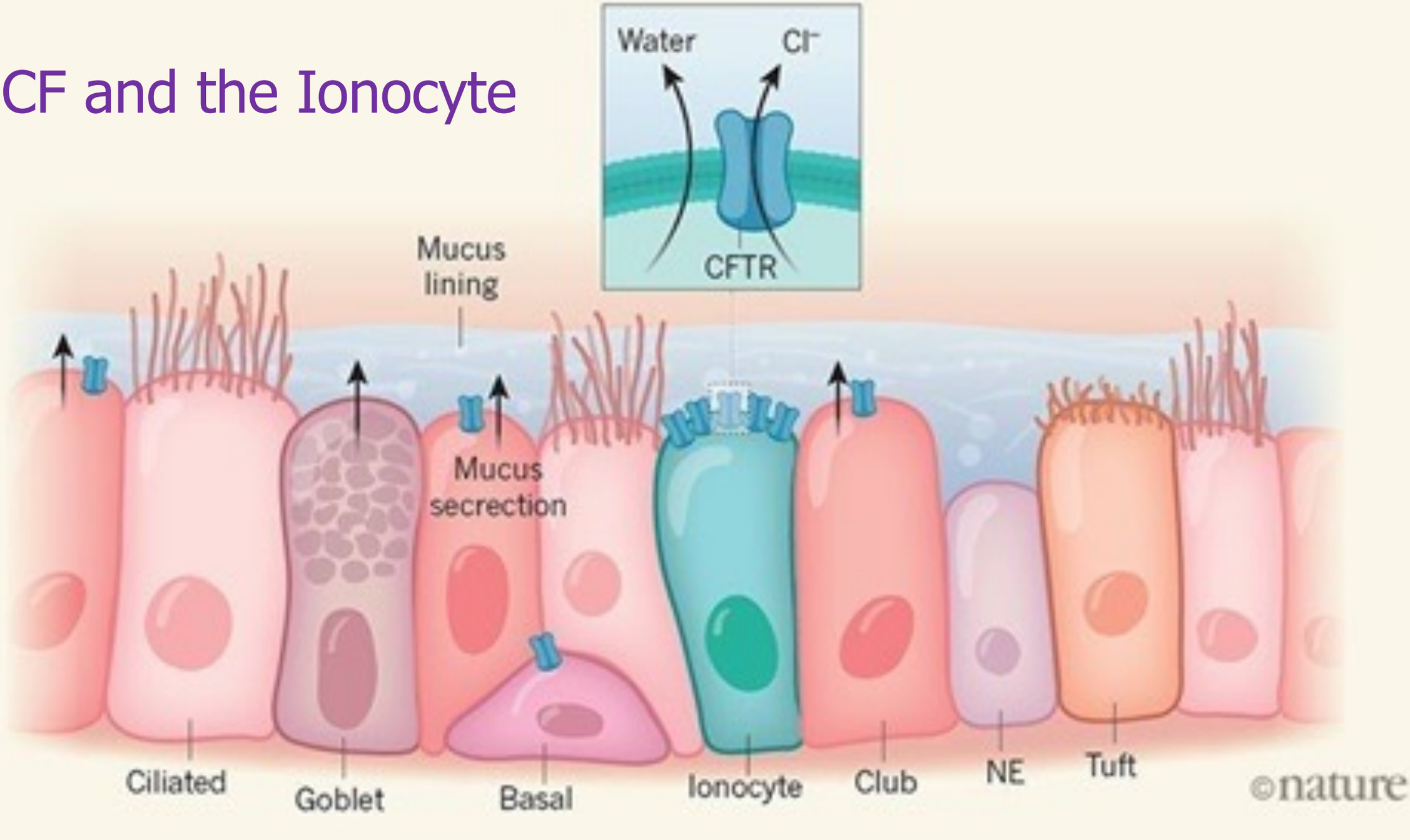
Minimal Function

Residual Function

	Normal	Class I	Class II	Class III	Class IV	Class V
DESCRIPTION	CFTR is created, reaches cell surface and functions properly, allowing transfer of chloride and water.	No functional CFTR created.	CFTR protein is created, but misfolded, keeping it from reaching the cell surface.	CFTR protein is created and reaches cell surface, but does not function properly.	The opening in the CFTR protein ion channel is faulty.	CFTR is created in insufficient quantities.
EXAMPLES		G542X W1282X R553X	F508del N1303K I507del	G551D S549N V520F	R117H D1152H R347P	3849+10kbC->T 2789+5G->A A455E

Adapted from: http://www.umd.be/CFTR/W_CFTR/gene.html

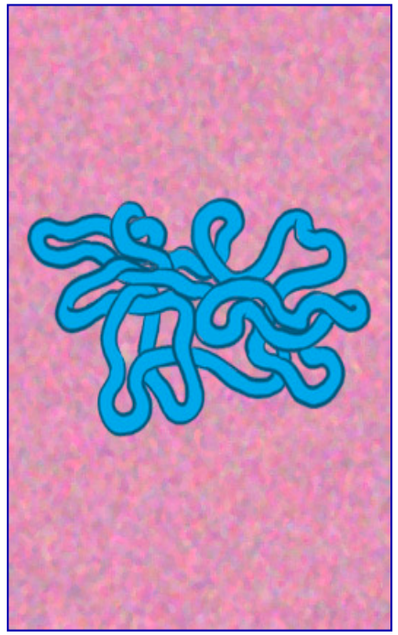
CF and the Ionocyte



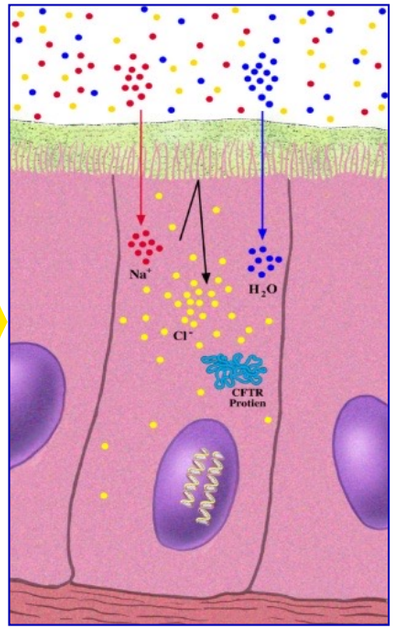
CF Pathophysiology

Abnormal Gene

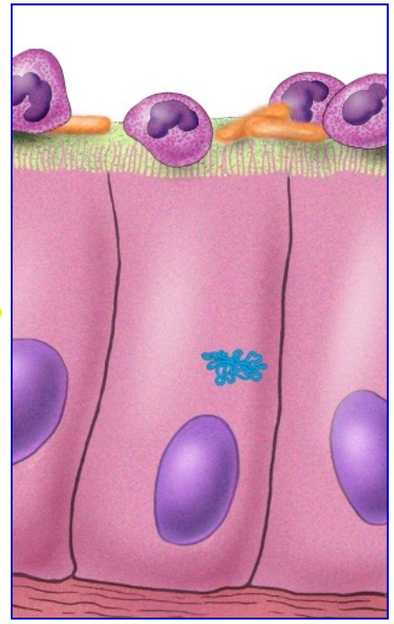
Abnormal Protein



A Altered Ion Transport (Cl^- and $HC0^-_3$) & Abnormal Mucus



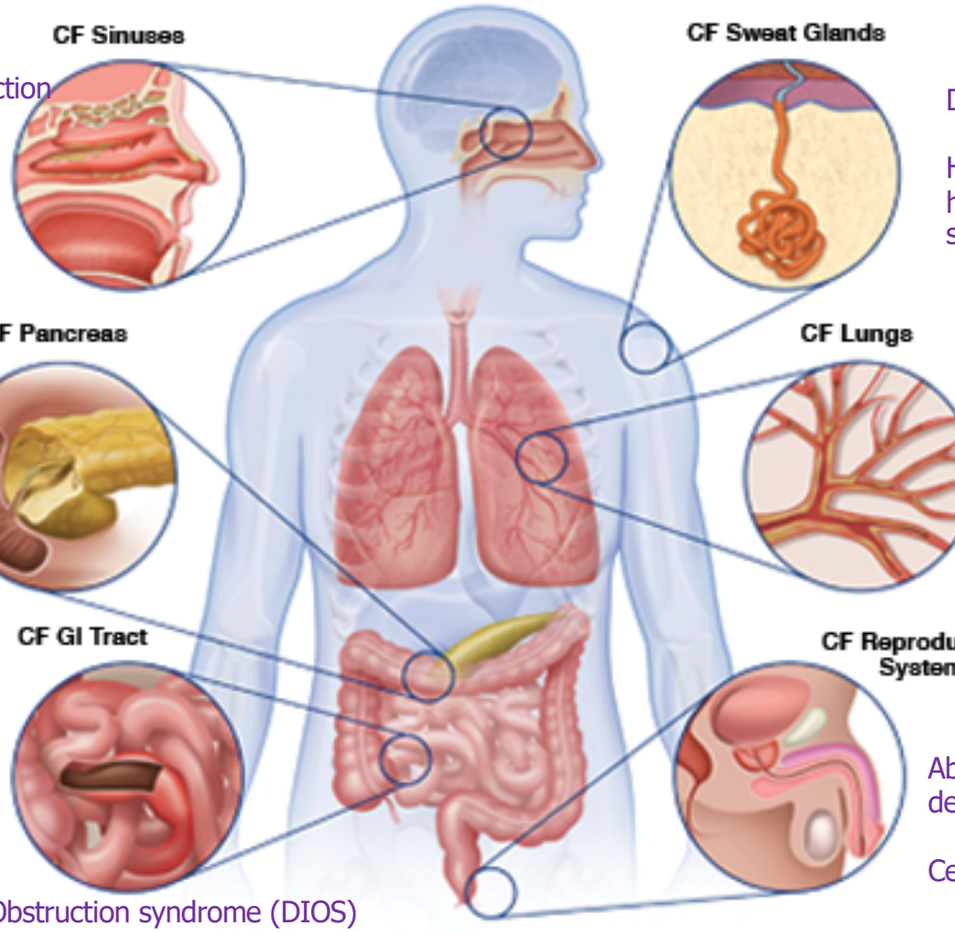
Infection & Inflammation



Organ Destruction & Respiratory Failure

CF - Multi-Organ Involvement

Nasal Polyps
Allergies
Chronic Sinus infection



Diagnostic test

Heat prostration and high salt content of sweat

Bronchiectasis
Chronic airway infection
Hemoptysis

CF Related DM
(>35% adults)
Pancreatic insufficiency and malnutrition

Absence or atresia of vas deferens

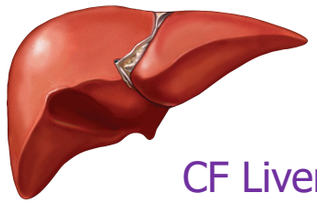
Cervical mucus/low pH

Meconium ileus
Distal Intestinal Obstruction syndrome (DIOS)

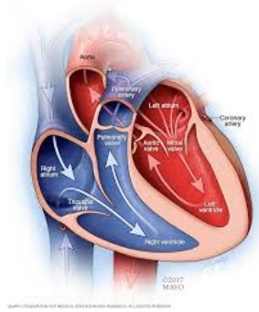
https://www.cftrscience.com/?q=CF-morbidity

Pulmonary Disease is major cause of morbidity and mortality

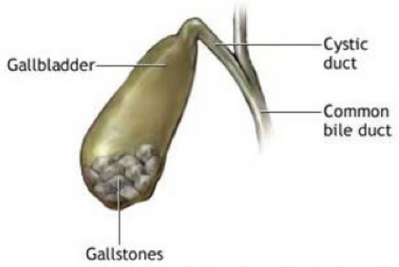
CF - Multi-Organ Involvement (Cont'd)



CF Liver Disease
(5% with PHTN)

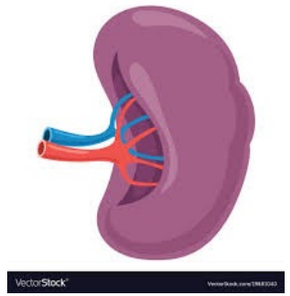


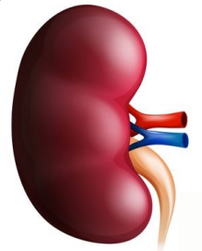
Pulmonary HTN and
Cor pulmonale



CF Gall Bladder
(cholelithiasis)

Splenomegaly
and splenic
infarcts



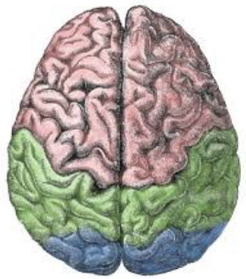


Nephrotoxic Meds
(immune complex
deposition)

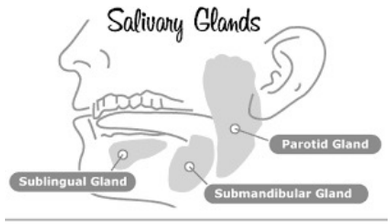
Ototoxic Meds
(CFTR in cochlea)

Indirect

CF Bone Health
(osteopenia and osteoporosis)



Arnold-Chiari Malformation



Salivary duct
plugging and stones

CF Mental
Health
(depression and
anxiety)

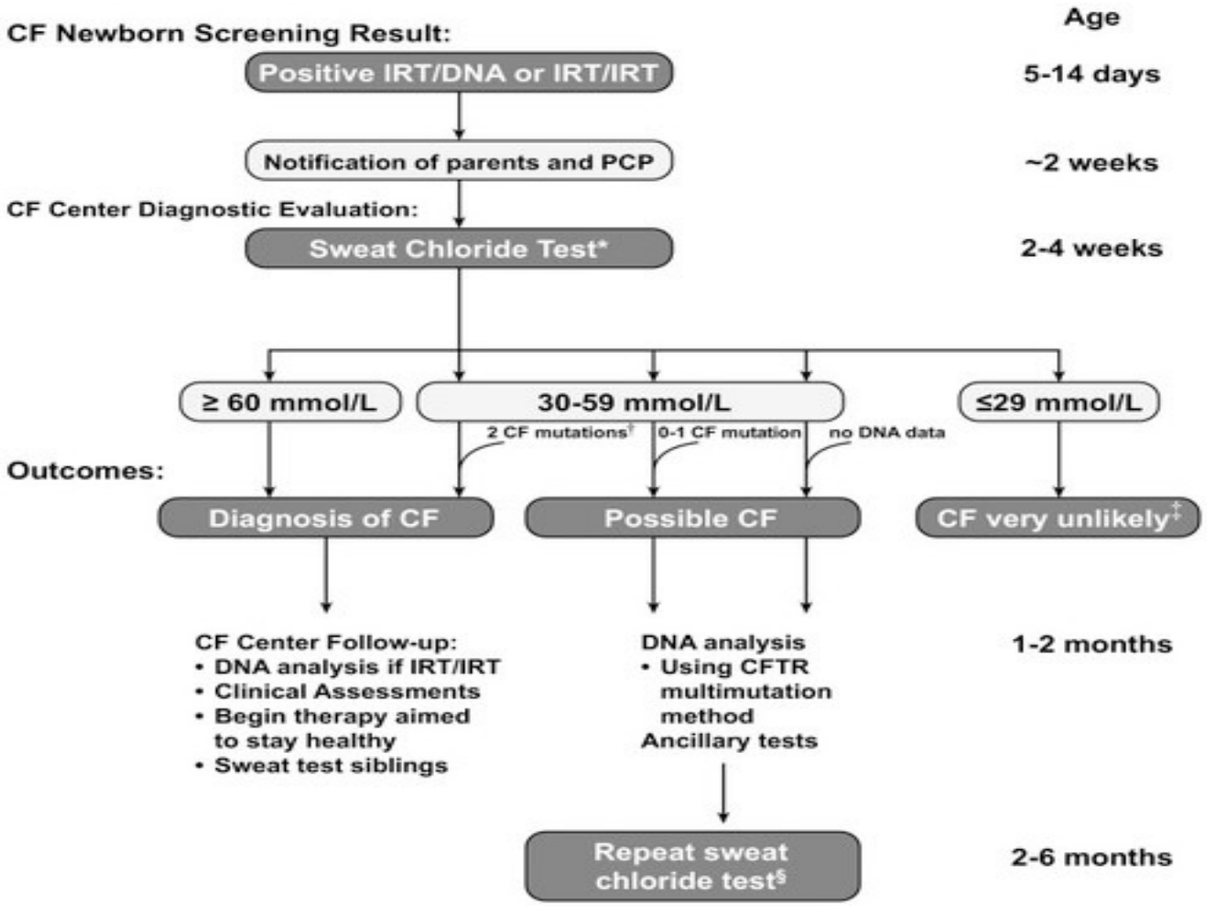
Patient Case

General information	
Age at diagnosis:	62 years
Current age:	62 years
Sex (M/F):	M
Genotype:	**F508Del/R117H**
Sweat chloride:	**68 mmol/L**
Lung function:	71% (initial)
Medical background (e.g. exacerbations/infection history):	
Last 2 years Hemoptysis 1-2 teaspoon with exacerbations	

Comorbidities:
Chronic Cough, Recurrent Bronchitis, Obstructive Sleep Apnea, Hypercholesterolemia, Hypertension, GERD, Prostate Ca s/p prostatectomy, Morbid obesity
Lifestyle/circumstance:
Decreased activity, desk job
CFTR Treatment:
Eligible for ivacaftor, a CFTR modulator **(prior to elexacaftor/tezacaftor/ivacaftor approval)**
Other
Never smoked No Children Family History of Colon cancer

CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

Diagnosis of Cystic Fibrosis



(J Pediatr 2008;153:S4-S14)

* If the baby is at least 2kg and more than 36 weeks gestation at birth, perform bilateral sweat sampling/analysis with either Gibson-Cooke or Macroduct® method; repeat as soon as possible if sweat quantity is less than 75 mg or 15 µl, respectively.

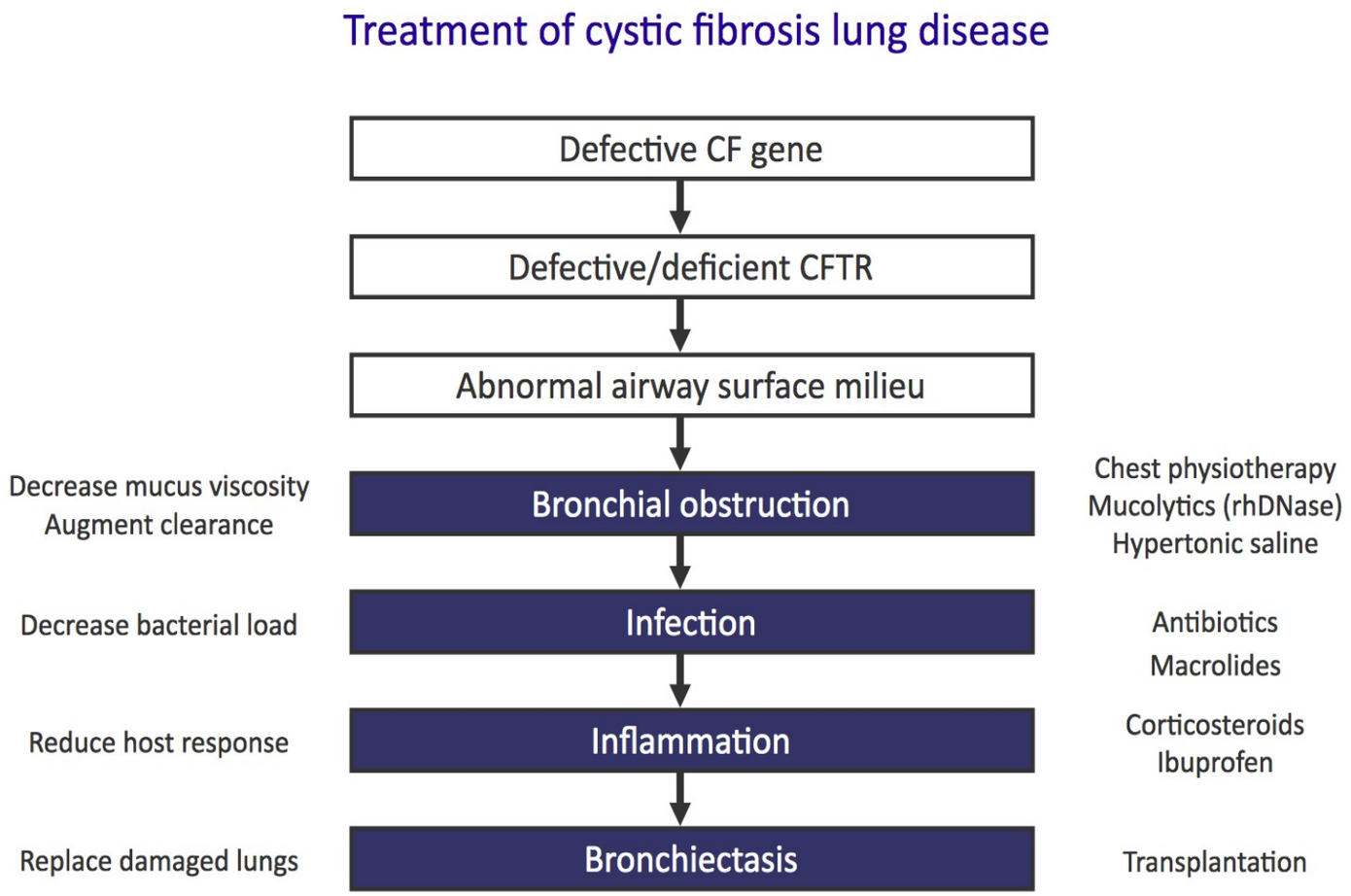
† CF mutation refers to a CFTR mutant allele known to cause CF disease.

‡ The disease is very unlikely; however, if there are 2 CF mutations in trans, CF may be diagnosed.

§ After a repeat sweat test, further evaluation depends on the results as implied above.

Therapeutic Approaches for CF Lung Disease

Davis PB, et al J Respir Crit Care Med. 1996;154:1229.



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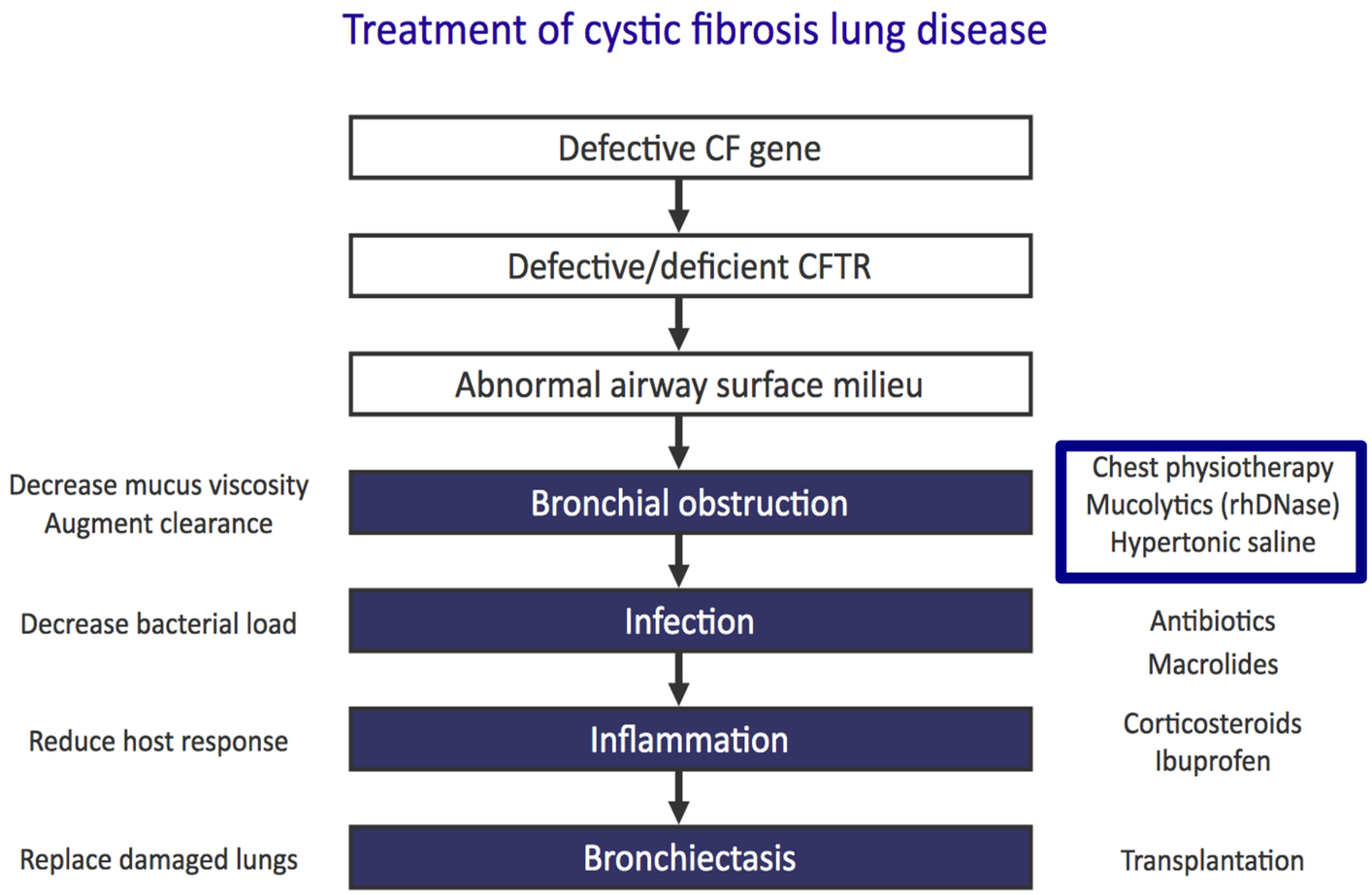


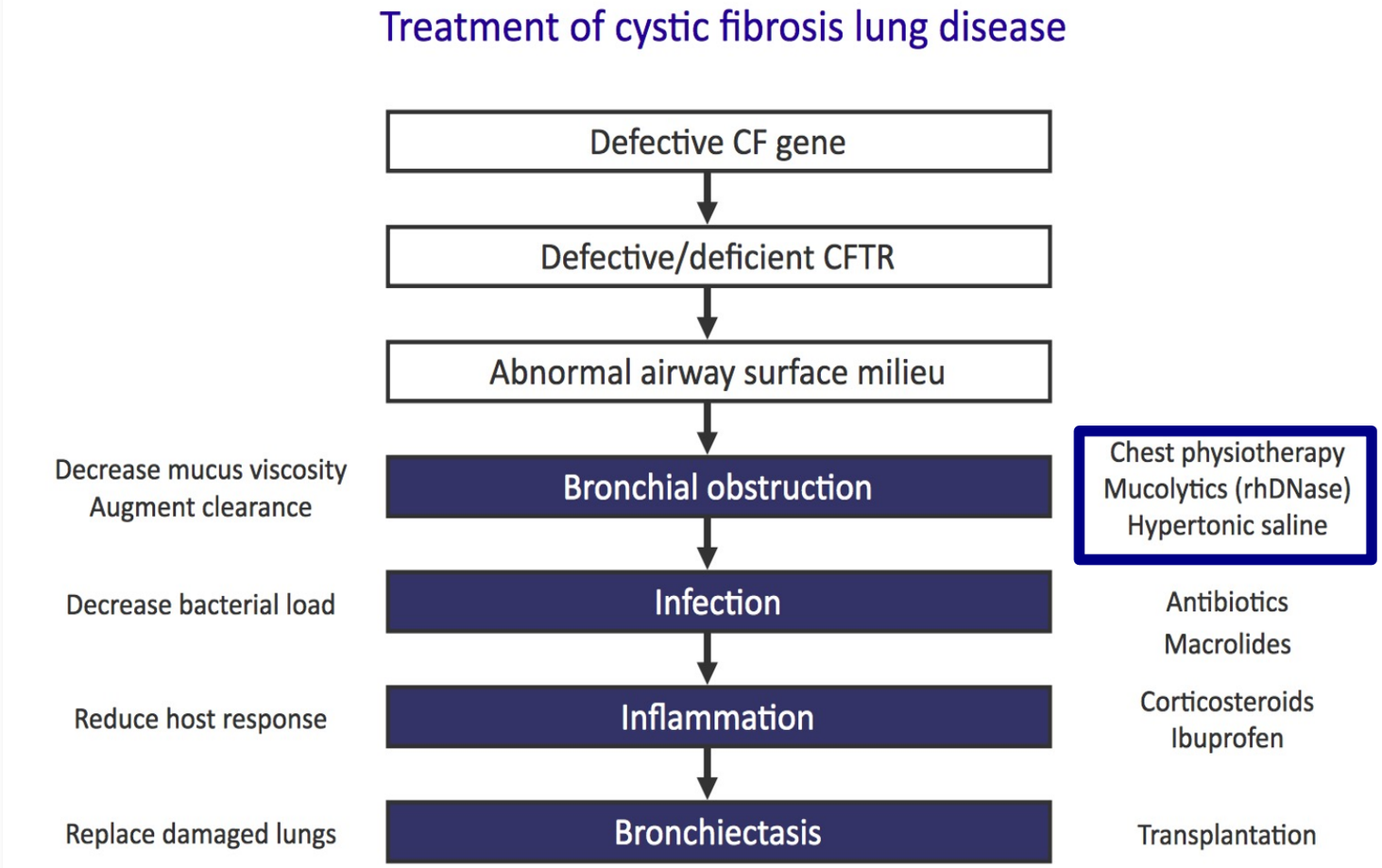
Therapeutic Approaches for CF Lung Disease

Davis PB, et al J Respir Crit Care Med. 1996;154:1229.

- High Frequency Chest Wall Compression (Vest)
- Manual Percussion and Drainage
- Positive Expiratory Pressure Device (PEP)
- Active Cycle Breathing and Autogenic drainage
- Exercise
- Others

Therapeutic Approaches for CF Lung Disease

Davis PB, et al J Respir Crit Care Med. 1996;154:1229.



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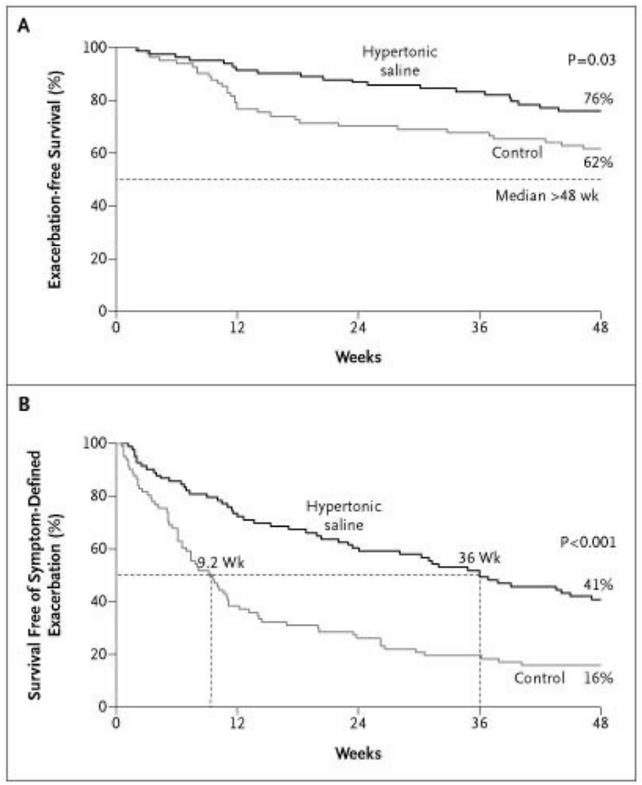
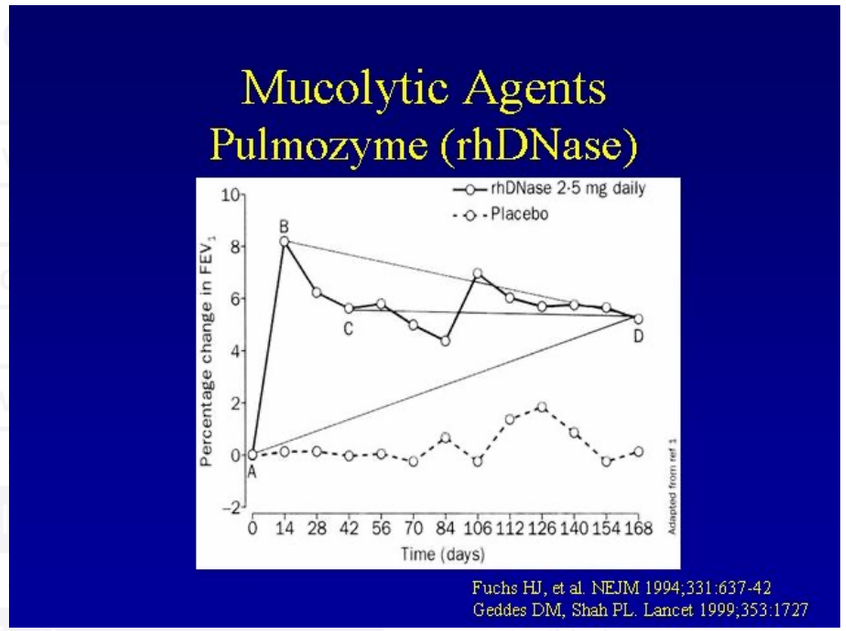
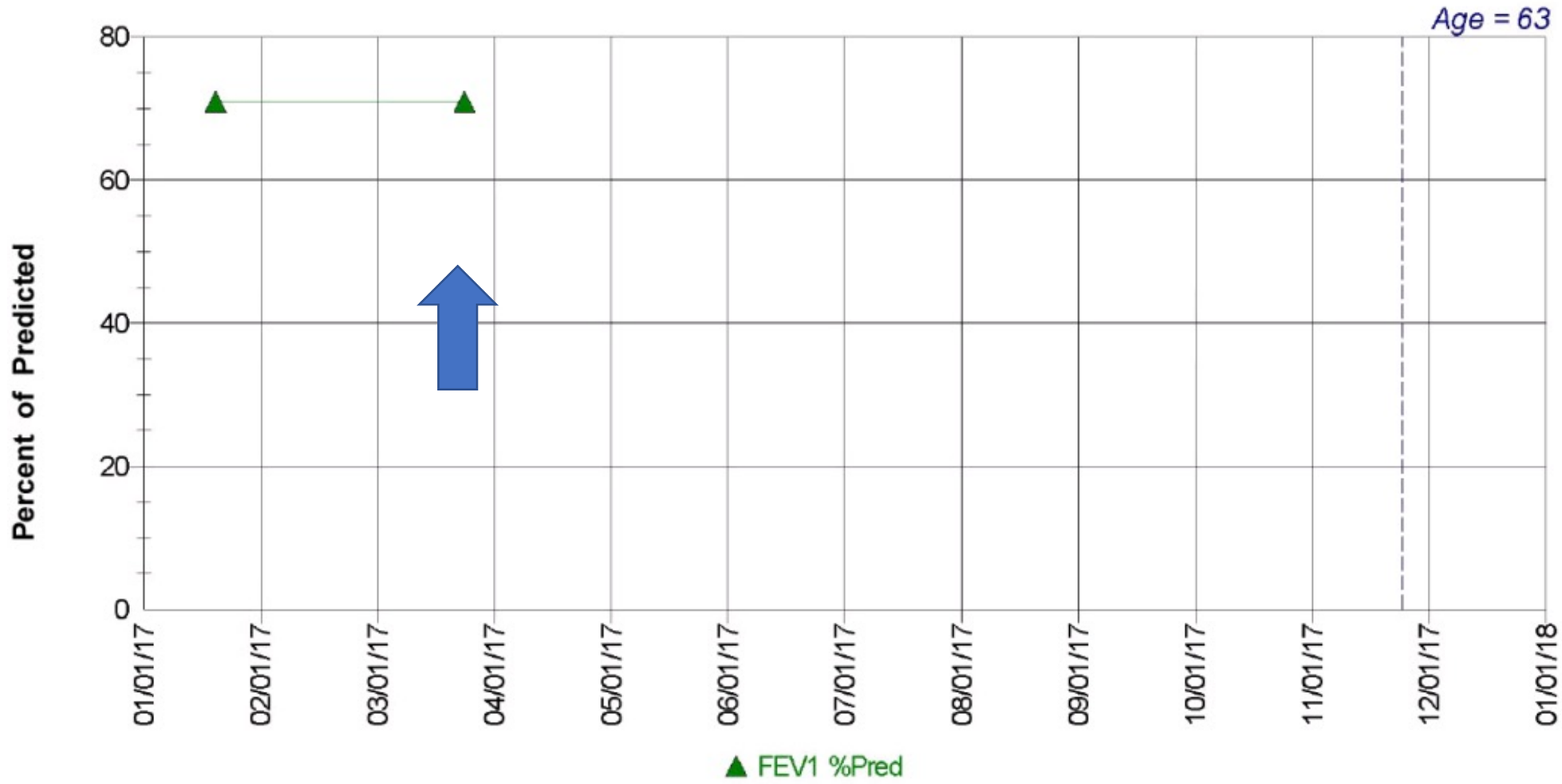


- Hypertonic Saline (7%)
- Twice daily

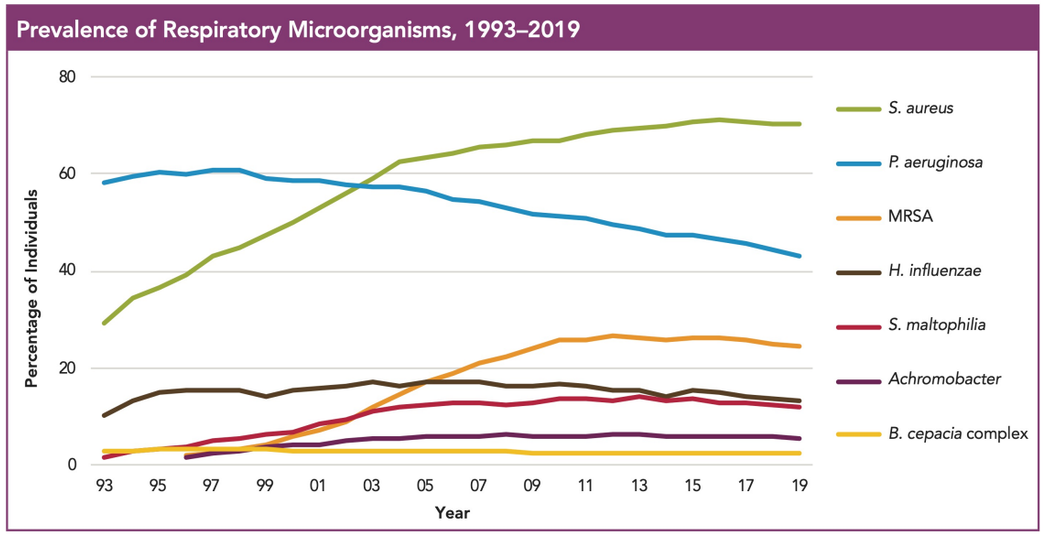


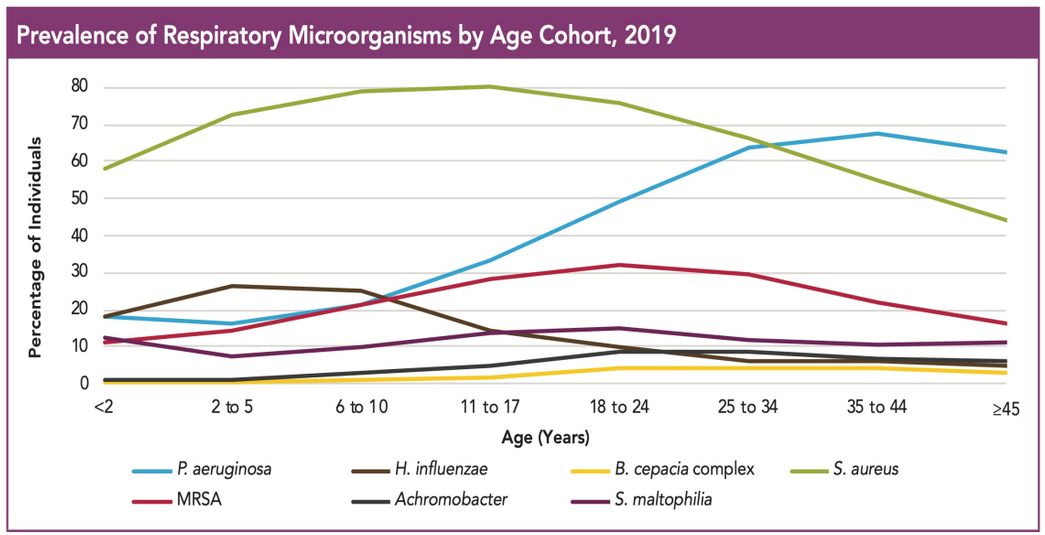
- Dornase alpha
- Once daily

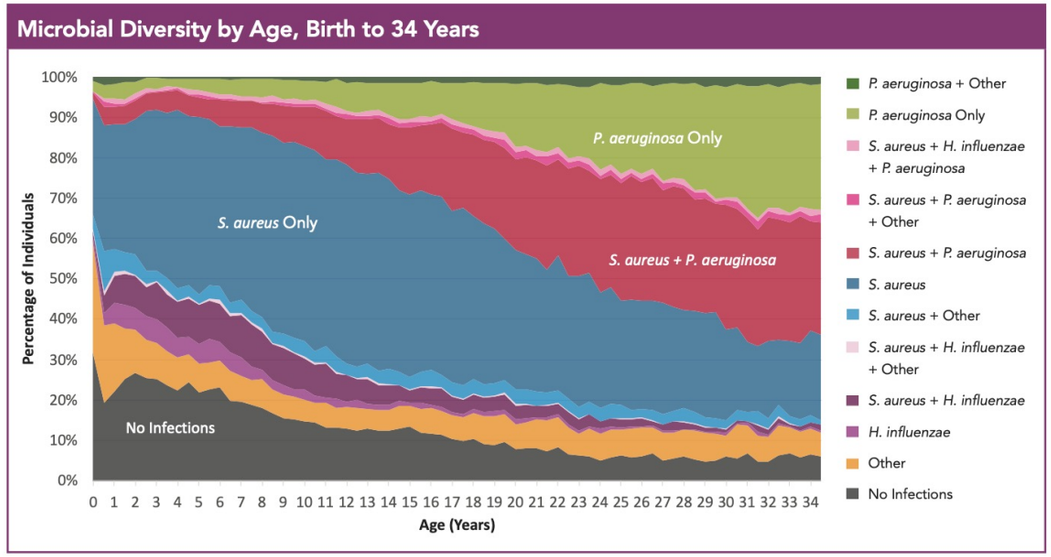
Patient Case – 62 year old newly diagnosed with CF



Bacterial Epidemiology in CF



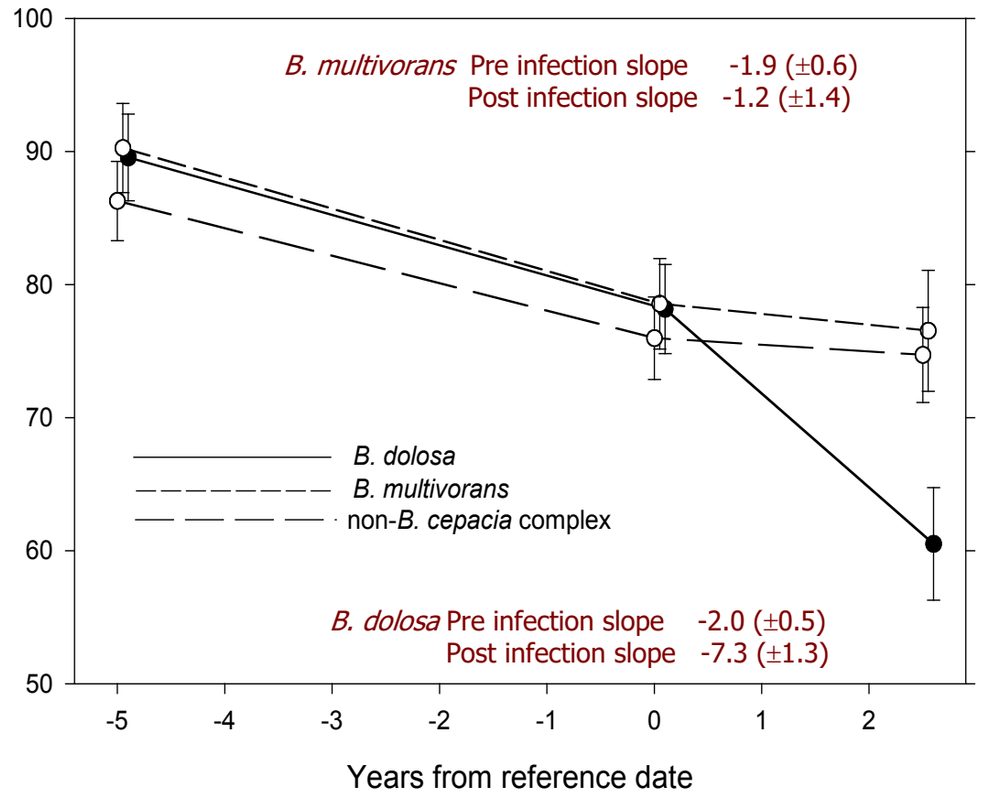




CFF 2019 Annual Registry Report

Preventing Infection and consequences of *B. dolosa* transmission

- Infection prevention and control is the most effective way to prevent new infections in CF



Kalish, Waltz et al. AJRCCM 2006

Therapeutic Approaches for CF Lung Disease

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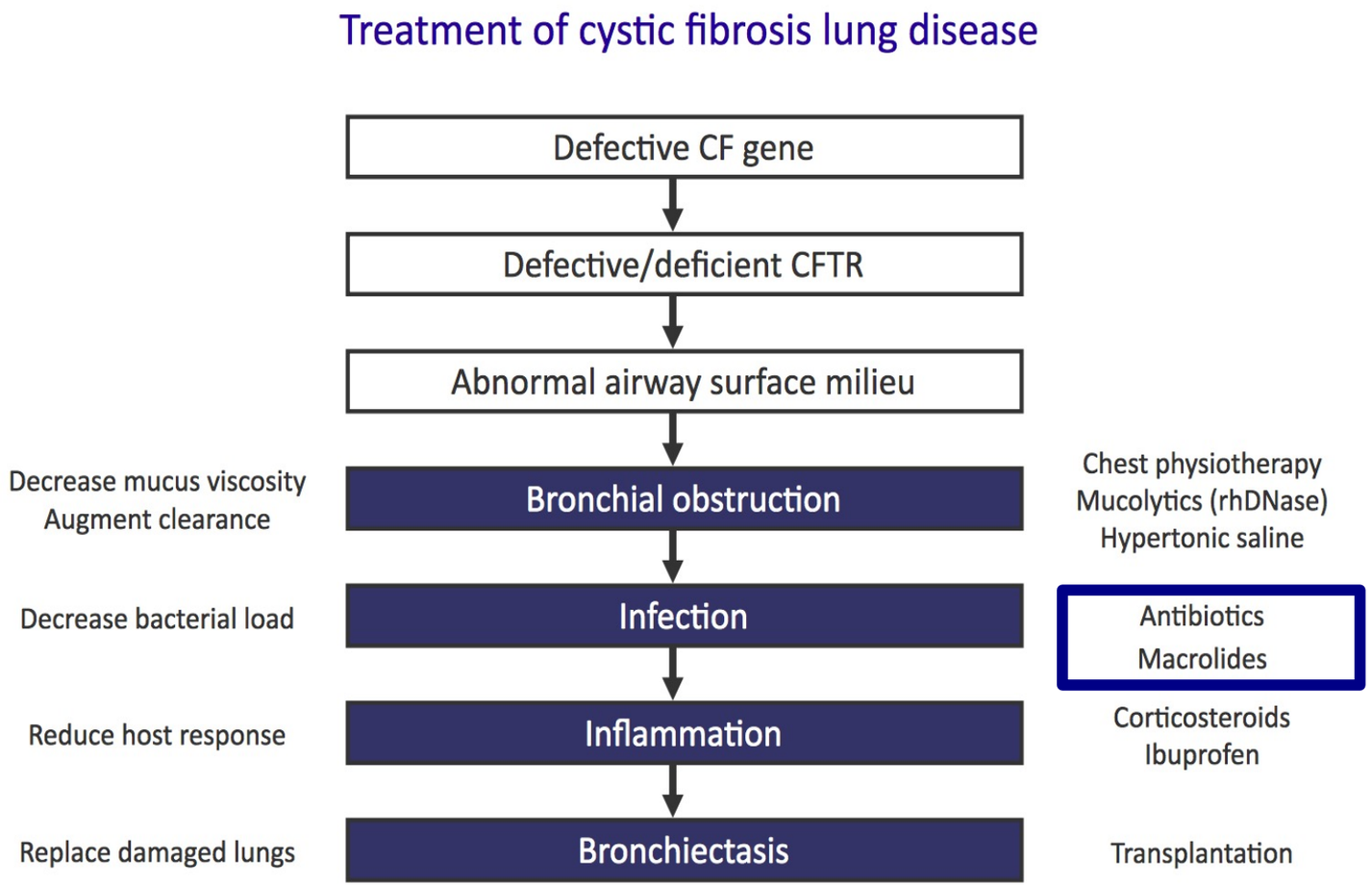

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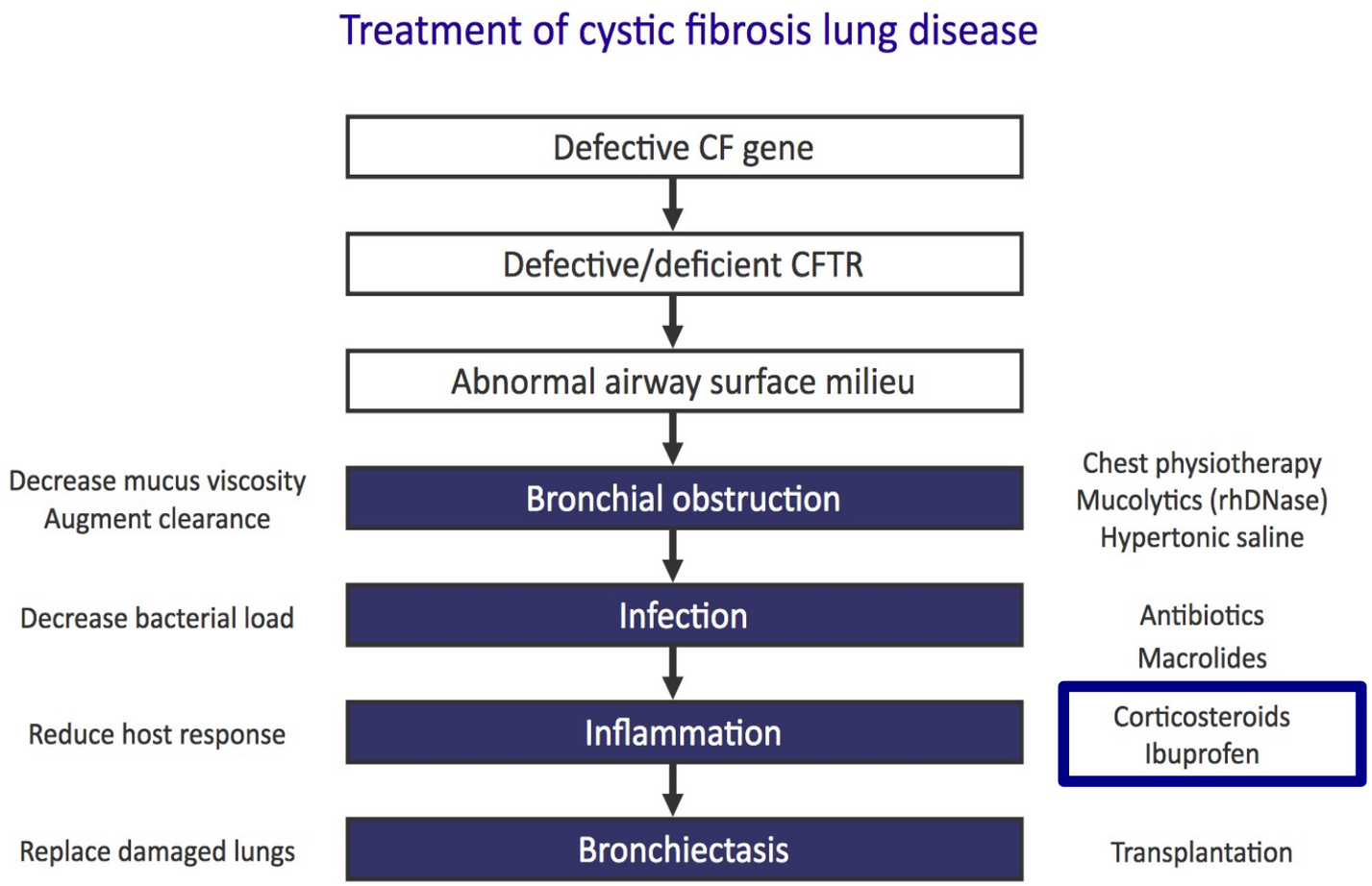


Therapeutic Approaches for CF Lung Disease

Davis PB, et al J Respir Crit Care Med. 1996;154:1229.

Systemic/Intravenous antibiotics

- **once daily aminoglycoside dosing with AUC monitoring**
- **prolonged infusion beta lactams**

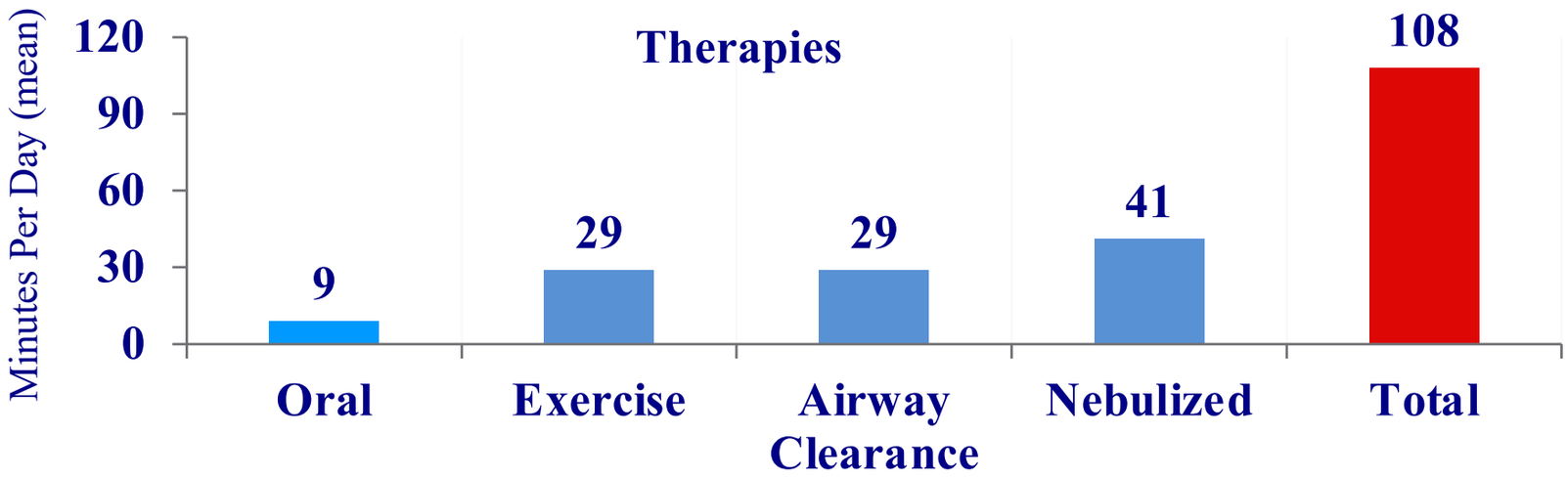
Chronic Therapies for Maintenance of Lung Health

Grade A Recommendation (High Benefit/Substantial)	**Grade B Recommendation (Mod Benefit/Substantial)**	**No Recommendation (Insufficient Evidence)**

• Inhaled Tobramycin
  • Mod-severe disease
• Dornase Alfa
  • Mod-severe disease
• Inhaled aztreonam
  • Mod-severe disease
• CFTR Modulators *(modified)*
  • (F508del and other eligible mutations)
	• Inhaled Tobramycin
	  • Mild disease
	• Dornase Alfa
	  • Mild disease
	• Inhaled aztreonam
	  • Mild disease
	• Hypertonic Saline
	• Macrolides (PsA)
	• Ibuprofen (<18 yrs)
		• Other aerosalized abx
		• N-acetyl cysteine
		• Cromolyn
		• Inhaled cholinergics
		• Leukotrienes
		• Oral Steroids
		• Inhaled beta-agonist
		• Macrolides (no PsA)
		• Chronic oral Anti-Staph

Flume et al. Am J Respir Crit Care Med 2007;176:957-969
Mogayzel et al. Am J Respir Crit Care Med 2013; 187:680-689

High Treatment Burden in CF



Medications	Median (Range)
# of Oral Medications	3 (0-7)
# of Nebulized Medications	2 (0-5)
# of Inhaled Medications (MDI)	1 (0-4)
# of Total Medications	**7 (0-20)**

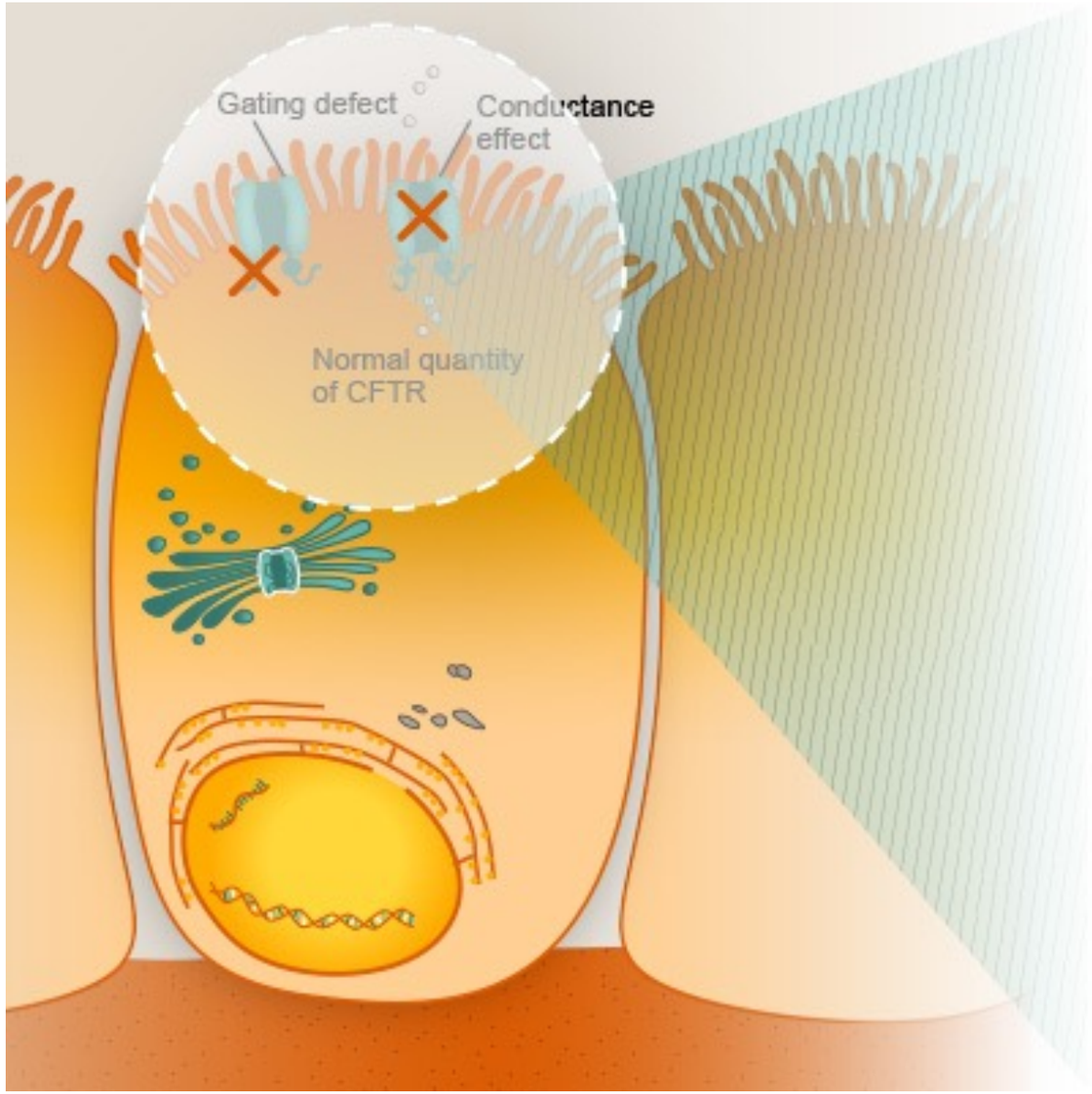
CF Related Observational and Interventional Studies

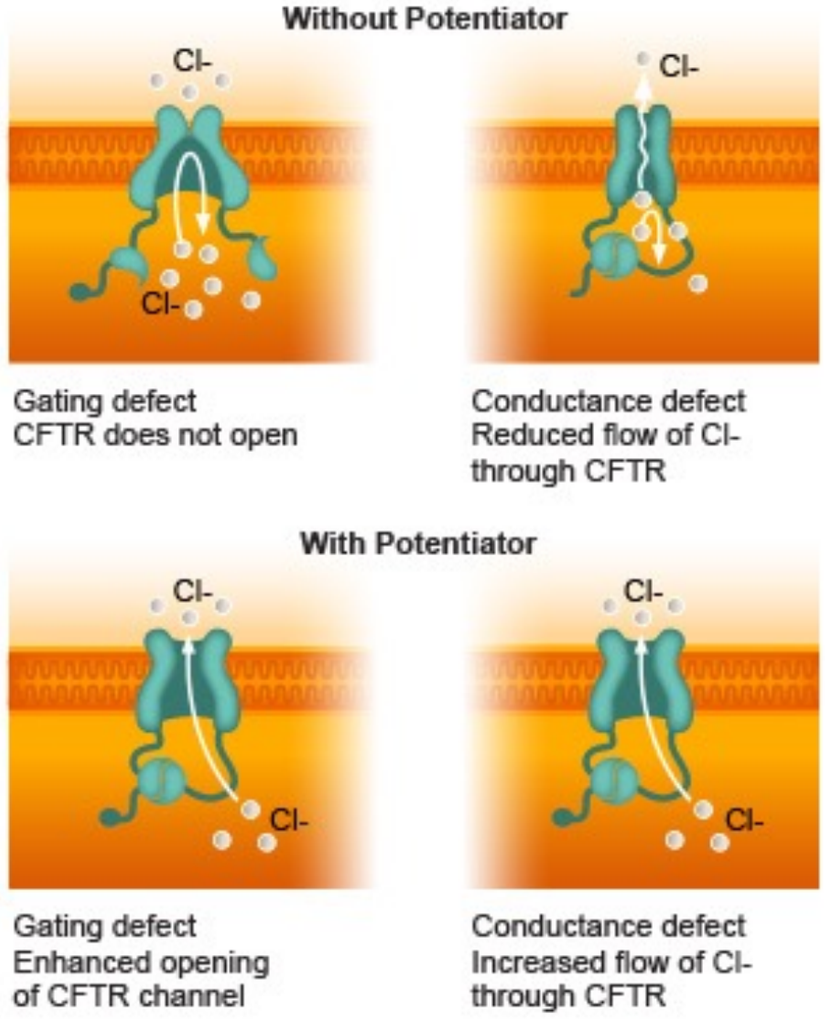
- PROMISE
  - Observational study looking at impact of triple combination CFTR modulator
- SIMPLIFY
  - Interventional study of discontinuing either Hypertonic Saline or Dornase Alfa while on triple combination CFTR modulator

Sawicki GS. *J Cyst Fibros.* 2009;8(2):91-96.

CF Care: At the Dawn of Precision Medicine

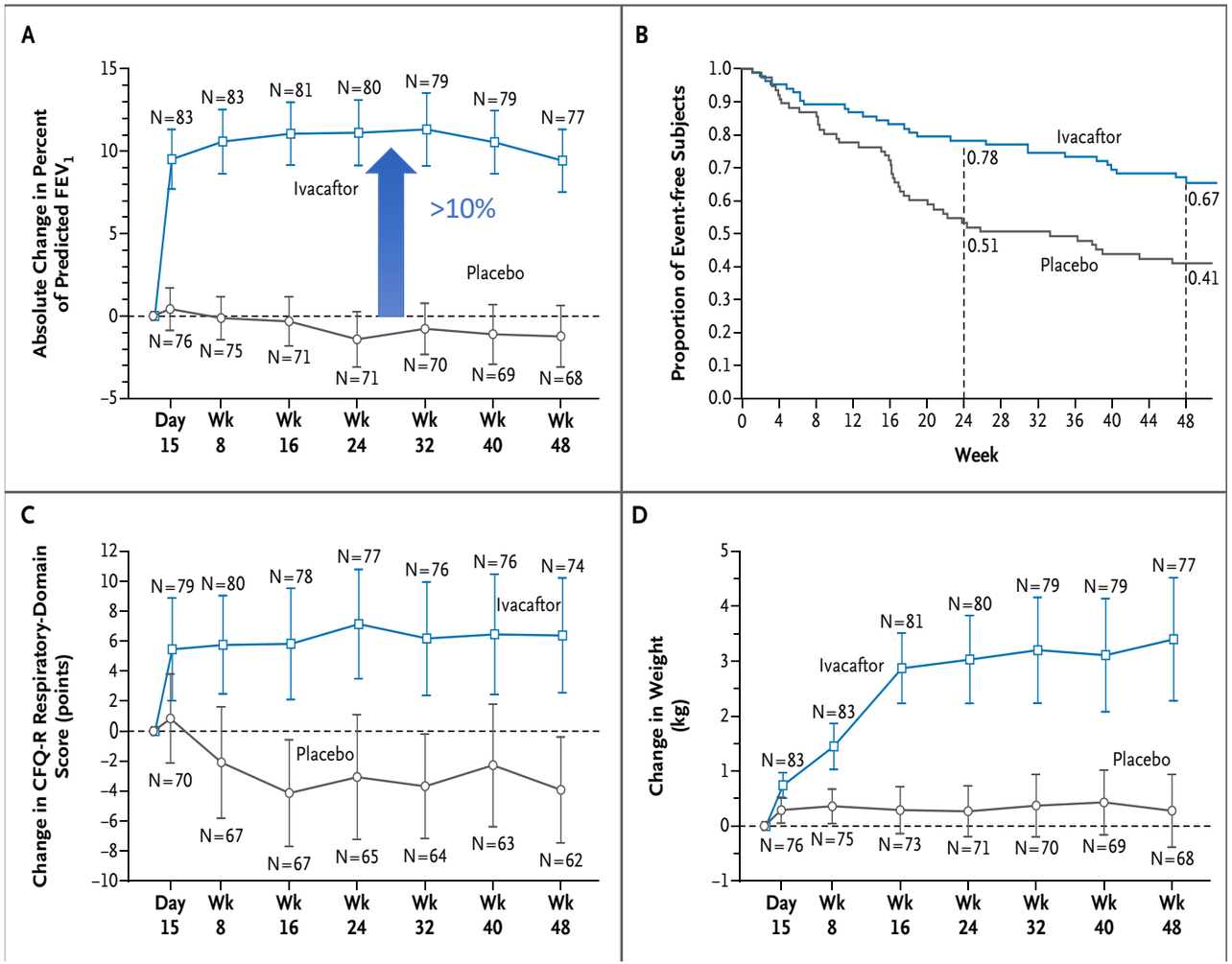
Precision Medicine - Potentiators



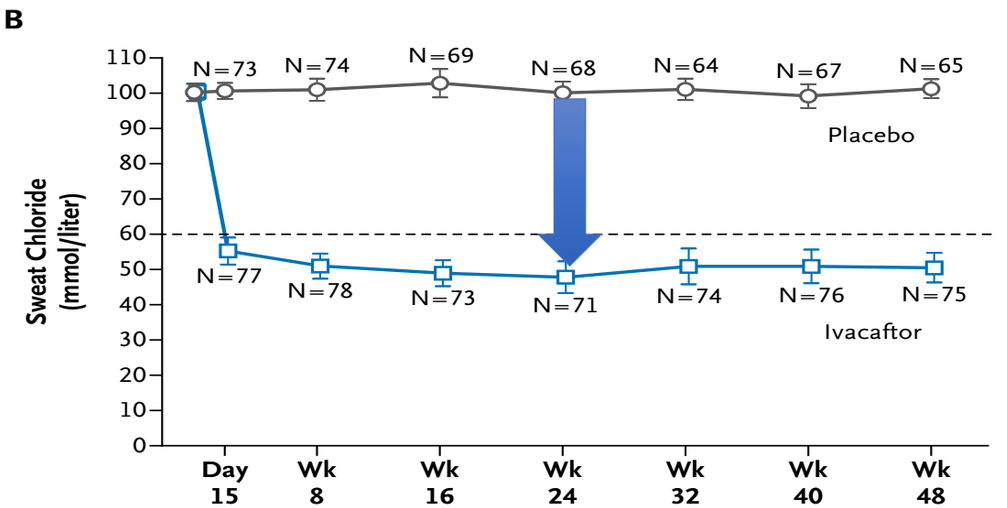


Courtesy of Vertex

Ivacaftor (Kalydeco) and health outcomes

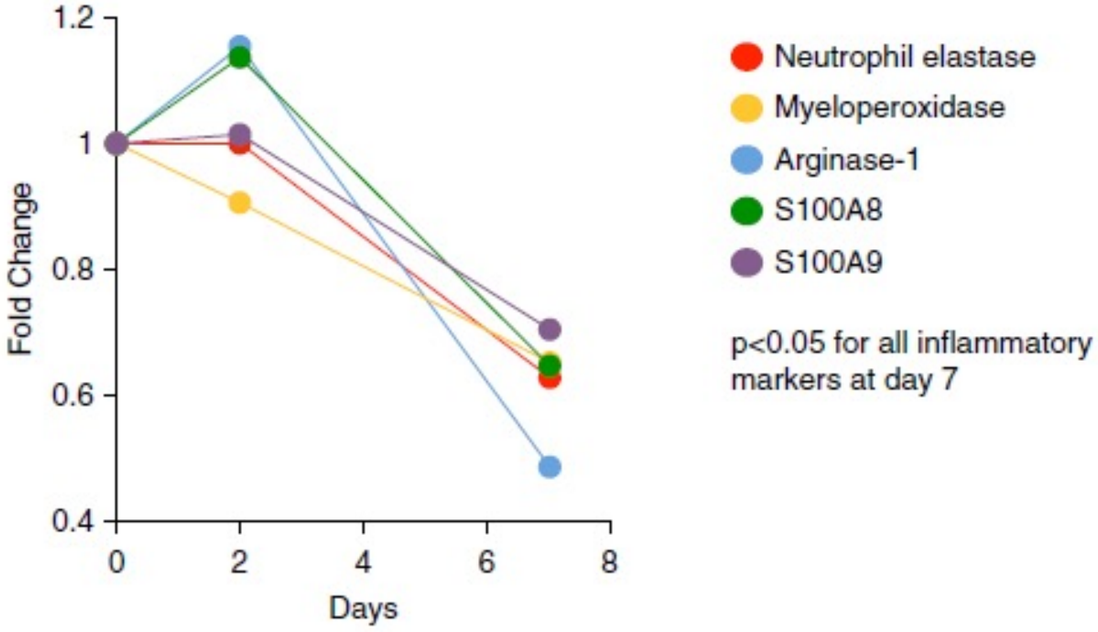


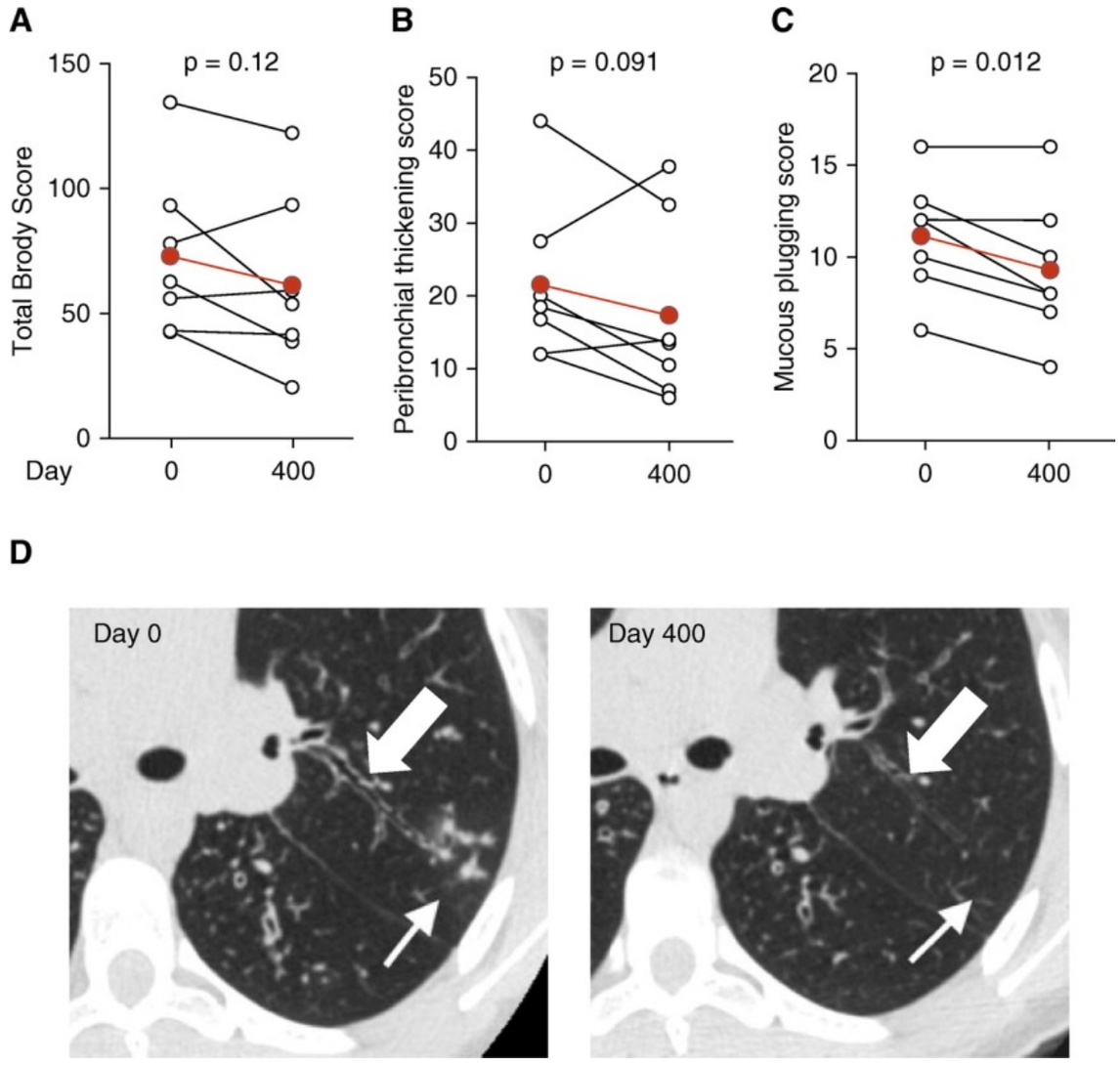
	Ivacaftor	Placebo
Absolute change from baseline through Week 24 in the ppFEV$_1$ (percentage points)	10.4	-0.2
Treatment difference (percentage points)	10.6 P<0.001	



CFQ-R, cystic fibrosis questionnaire respiratory; FEV, forced expiratory volume.
Ramsey BW et al. *N Engl J Med* 2011;365:1663–1672.

Single-center data on ivacaftor: Changes in sputum inflammation and CT scans





Hisert KB et al. *Am J Respir Crit Care Med* 2017;195(12):1617–1628.

Lung Health in the Longer Term: FEV_1 DECLINE

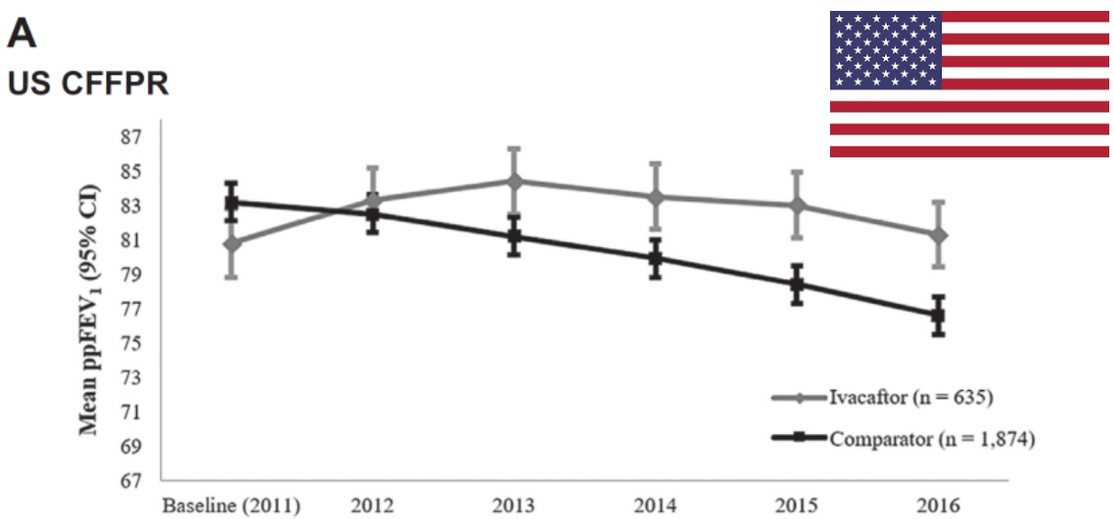
Contents lists available at ScienceDirect

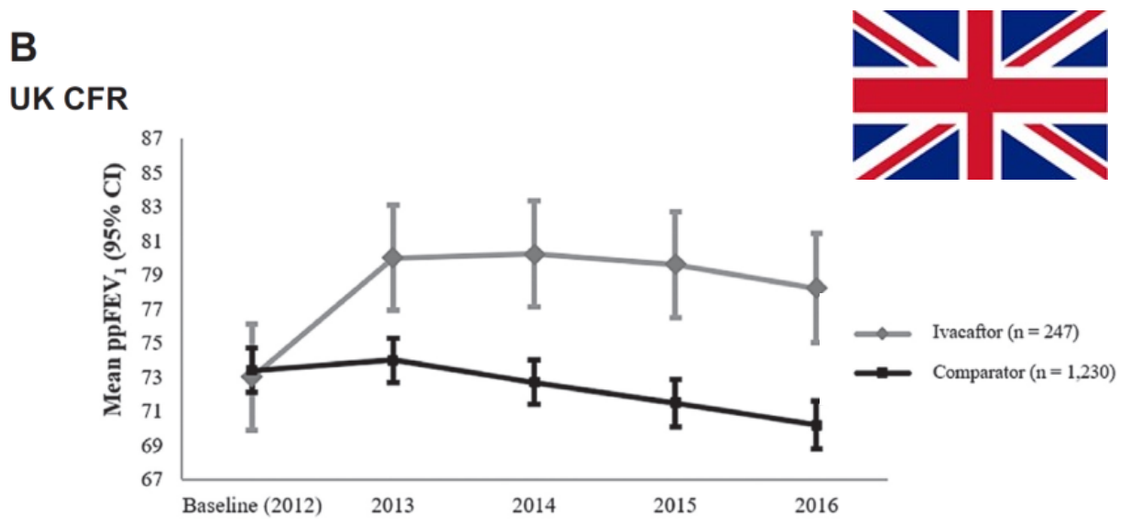
Journal of Cystic Fibrosis

journal homepage: www.elsevier.com/locate/jcf

Disease progression in patients with cystic fibrosis treated with ivacaftor: Data from national US and UK registries

Nataliya Volkova [a,*], Kristin Moy [a], Jennifer Evans [b], Daniel Campbell [a], Simon Tian [a], Christopher Simard [a], Mark Higgins [c], Michael W. Konstan [d], Gregory S. Sawicki [e], Alexander Elbert [f], Susan C. Charman [g], Bruce C. Marshall [f], Diana Bilton [g,h]





Significant improvements in survival and need for transplantation

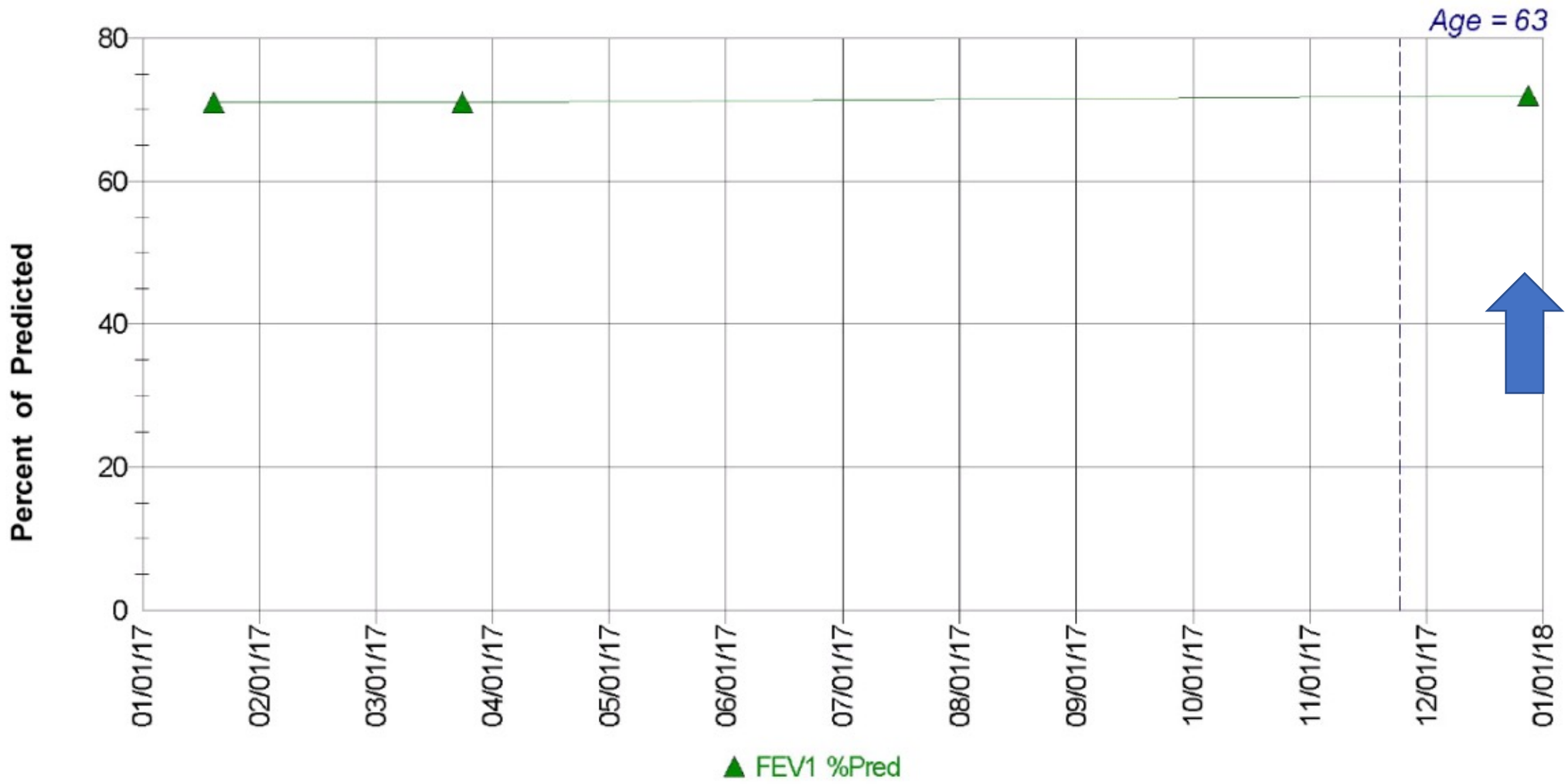
Patient Case

General information	
Age at diagnosis:	62 years
Current age:	62 years
Sex (M/F):	M
Genotype:	**F508Del/R117H**
Sweat chloride:	**68 mmol/L**
Lung function:	71% (initial)
Medical background (e.g. exacerbations/infection history):	
Last 2 years Hemoptysis 1-2 teaspoon with exacerbations	

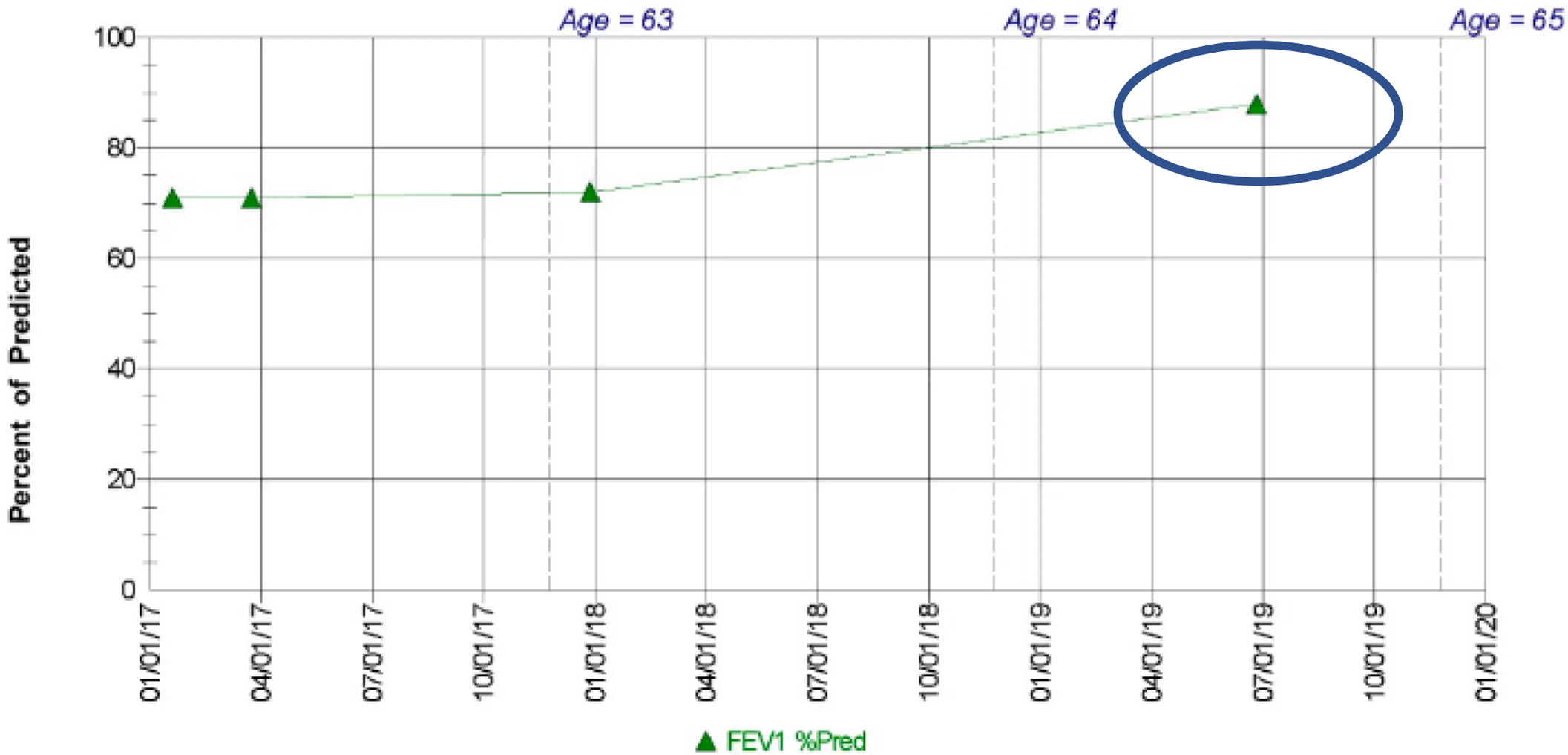
Comorbidities:
Chronic Cough, Recurrent Bronchitis, Obstructive Sleep Apnea, Hypercholesterolemia, Hypertension, GERD, Prostate Ca s/p prostatectomy, Morbid obesity
Lifestyle/circumstance:
Decreased activity, desk job
CFTR Treatment:
Eligible for ivacaftor
Other
Never smoked No Children Family History of Colon cancer

CFTR, cystic fibrosis transmembrane conductance regulator; GERD, gastroesophageal reflux disease.

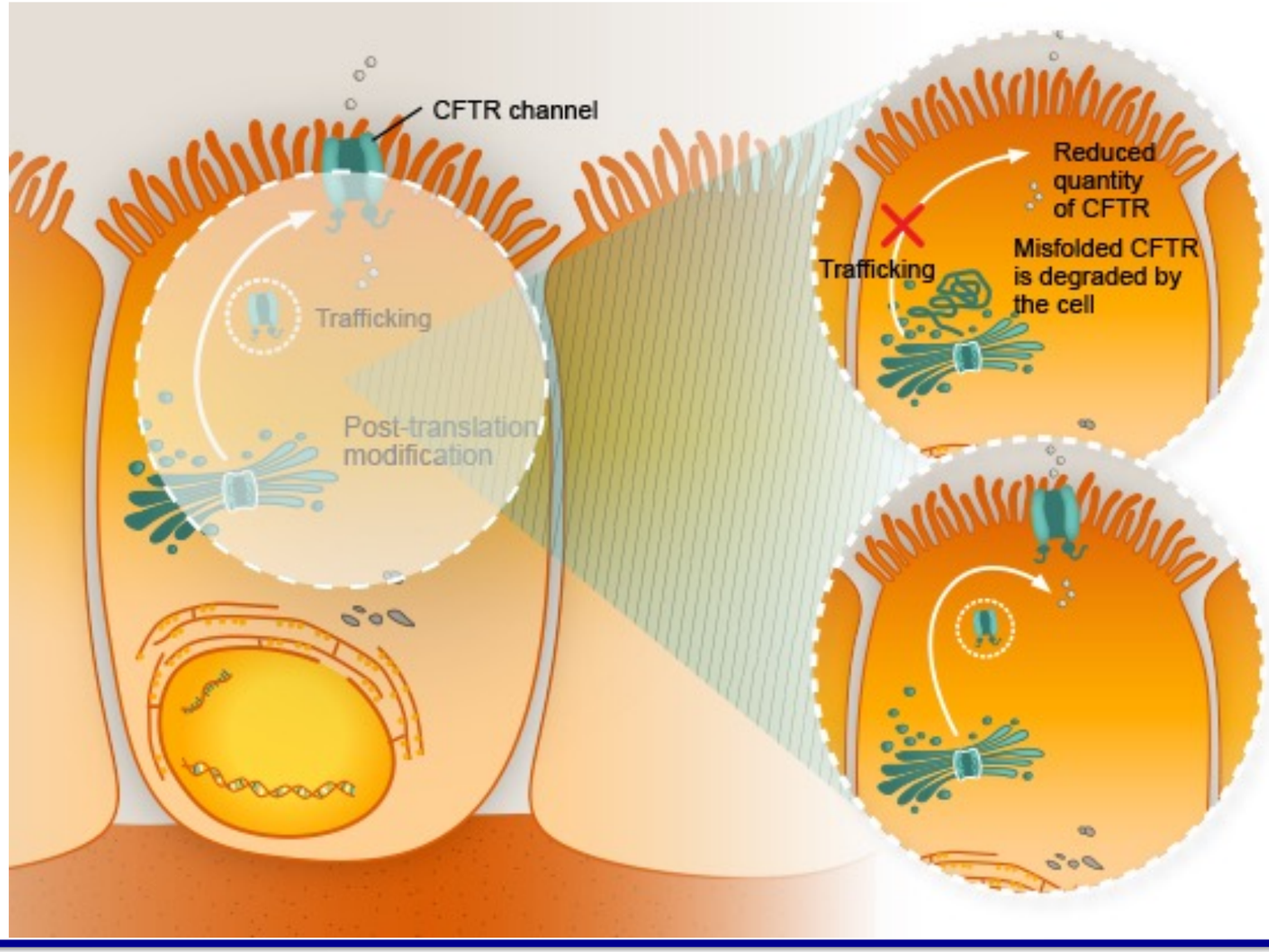
Patient Case



Patient Case



Precision Medicine - Correctors + Potentiator



Without Corrector

Mutation(s) in CFTR protein cause misfolding and degradadation of the protein

With Corrector

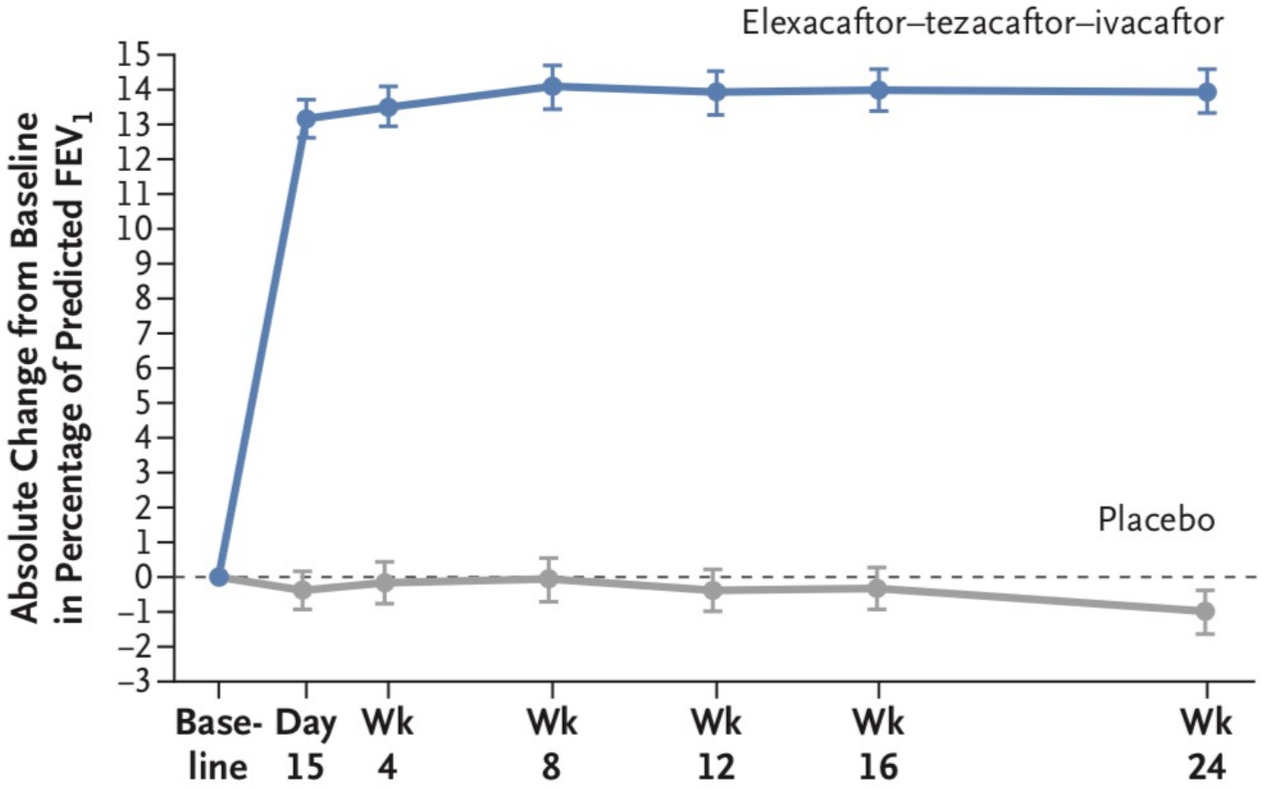
Correctors increase the surface density of CFTR at the membrane. They may also enhance the function of CFTR at the membrane

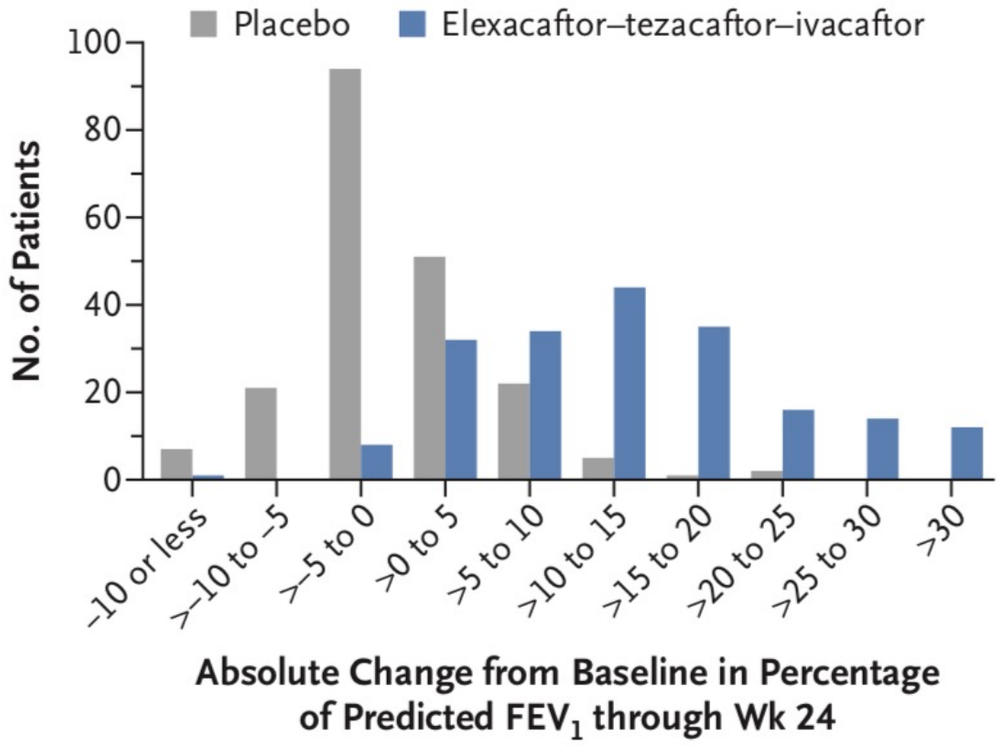
October 21, 2019

FDA Approved Trikafta
(elexacaftor/tezacaftor/ivacaftor)
for those with at least **one copy F508Del**

Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

Lung Function Response (FEV1)

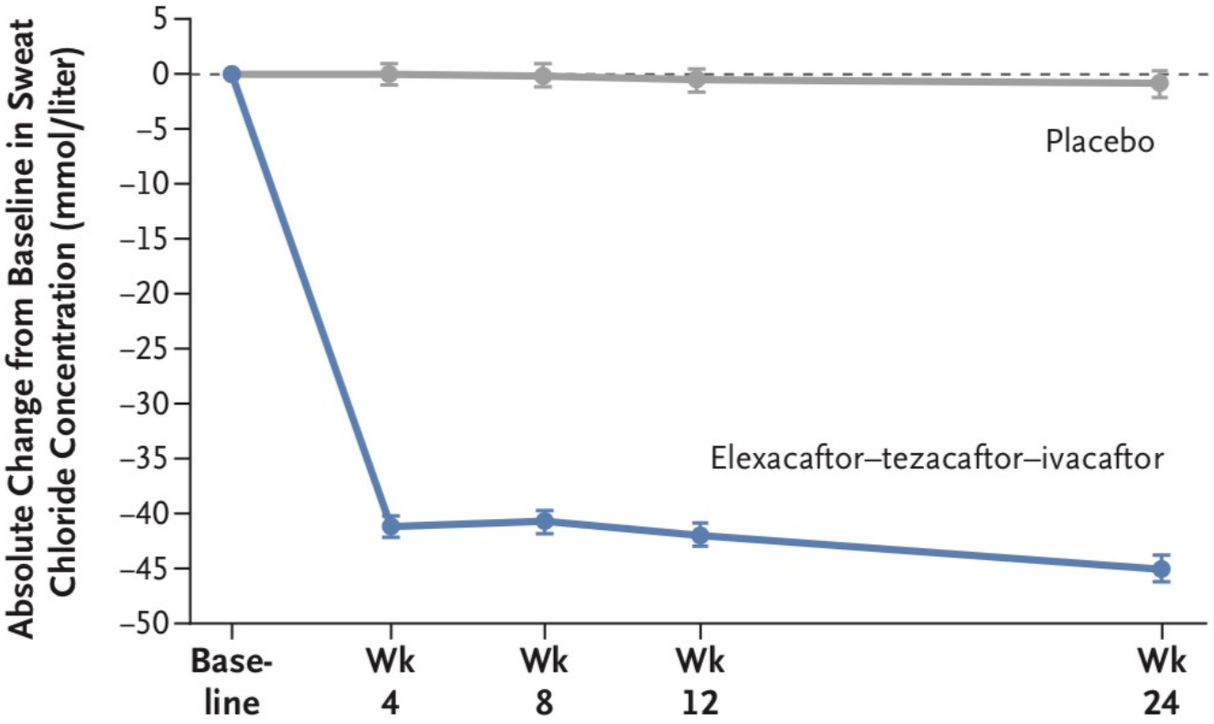


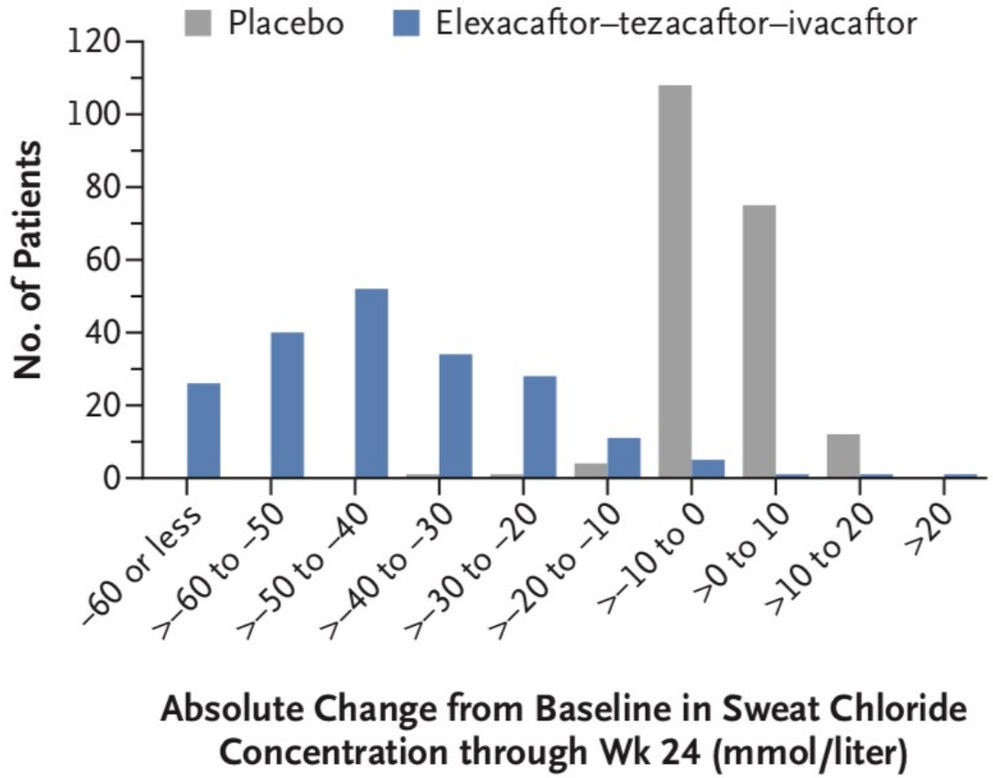


Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

Sweat Chloride Response (mmol/liter)

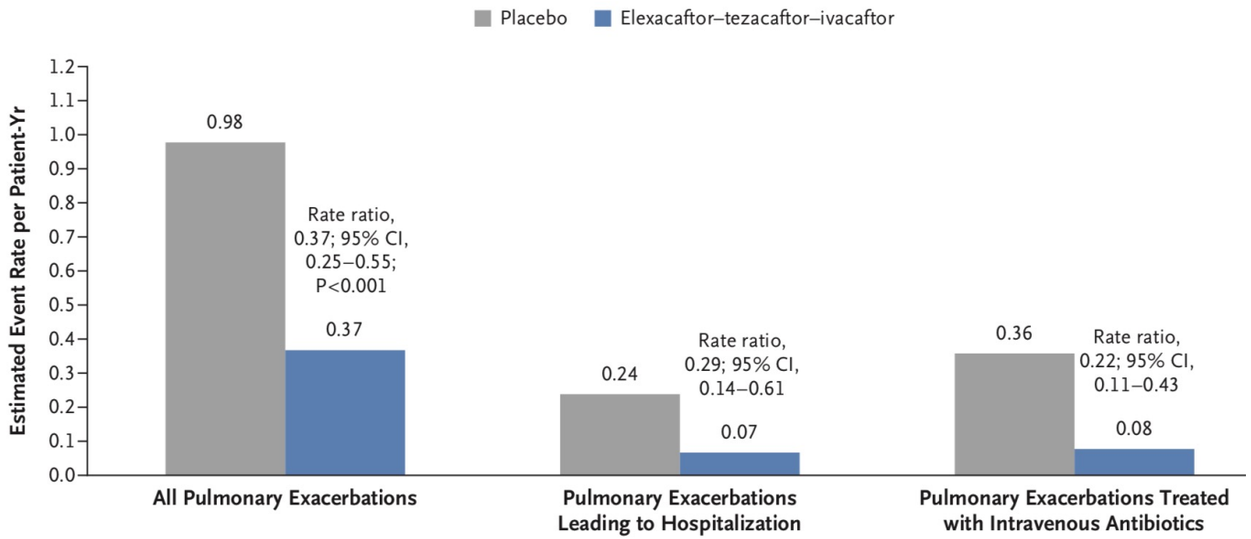


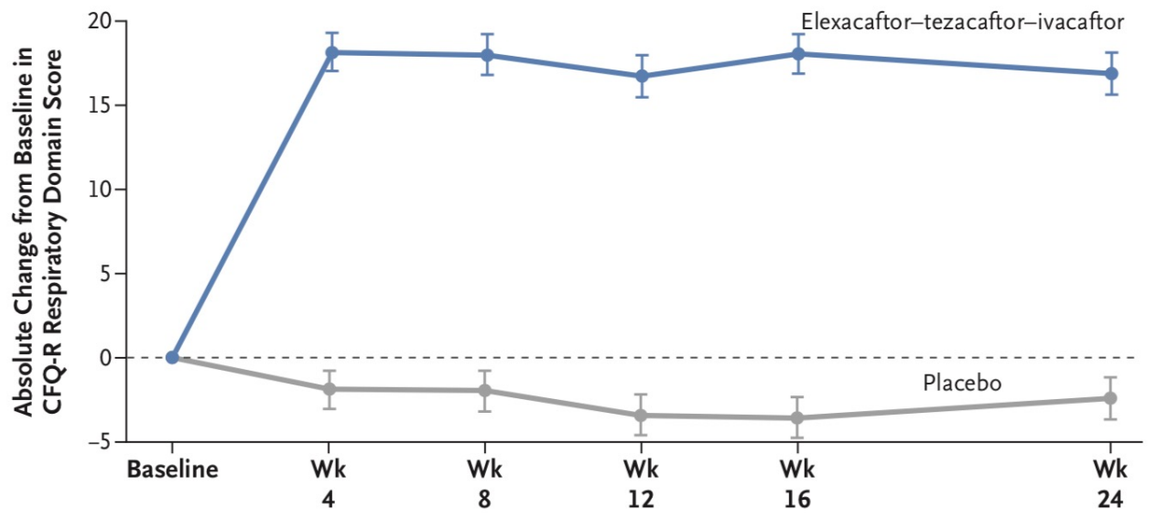


Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

Elaxacaftor/Tezacaftor/Ivacaftor (Trikafta)

Exacerbations and CFQ-R





Middleton, PG et al. *N Engl J Med* 2019:1-10.DOI 10.1056

So, Are We Done?

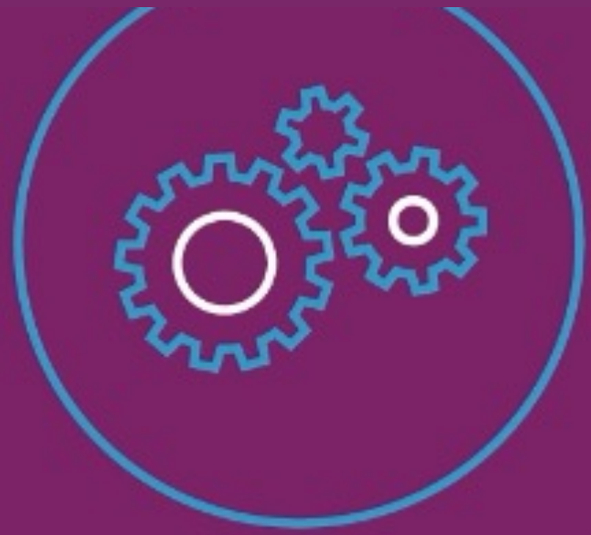
- No, more work to do:
  - Established disease:
    - ALD remains but observing some reversal
  - Pulmonary exacerbations:
    - Significantly reduced, not prevented
  - Chronic infection:
    - Some change but chronic infection model remains
  - Extrapulmonary effects
  - Extending use to younger patients
  - Sweat chloride still not fully normalized
  - 10% without a drug
  - Some unable to tolerate
  - Working on non-pulmonary complications
- Cost and regional differences in availability

CFF 2018 Commitment

- $100 Million Infection Research Initiative
- Industry and Academic Researches
  - Detection
  - Diagnosis
  - Prevention
  - Treatment
- Addressing the need to treat acute/chronic infections in era of increased risk of antibiotic resistance

Courtesy of CFF

REPAIR
CFTR PROTEIN



RESTORE
CFTR PROTEIN

FIX OR REPLACE
CFTR GENE

Future of CF Therapeutics

Courtesy of CFF

Summary Points

- CF is autosomal recessive disease that has a highly variable phenotypic expression among patients of all ages, particularly adults, with improved survival overall
- Diagnosis of CF is made by a combination of clinical manifestations, sweat chloride levels, CFTR mutation analysis
- Chronic airway infection with any number of organisms, but most typically *P.aeruginosa*, leads to progression of obstructive lung disease. NTM an increasing concern not discussed
- Precision medicine with new therapies involving small molecule potentiators and correctors, including a highly effective triple combination potentiator/correctors currently available to nearly 90% of patients
- Future CF therapeutics include gene editing and gene replacement, as well as focus on anti-microbials, anti-inflammatories, attention to nutrition and anticipating complications in a multi-disciplinary care team setting

Board Questions 1-4 based on Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #1 of hospitalization
  - Tachypnea, chest pain and worsening SOB

Question #1

- What is LEAST likely complication associated with this patient's presentation:
  - A) Pulmonary Embolism
  - B) Mucus plugging
  - C) Non-ST elevation MI
  - D) Pneumothorax

Continuation of Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #2
  - You are called to patient bedside due to 250cc of bright red blood.
  - Bleeding stopped on its own, VSS and patient describes chest discomfort on right side

Question #2

- What is LEAST helpful intervention:
  - A) Perform a bronchoscopy to determine whether bleeding coming from right or left lung
  - B) Ask patient to lie down with right side of chest down
  - C) Give Vitamin K while in process of checking PT/INR
  - D) Call interventional radiology for potential Bronchial artery embolization (BAE)
  - E) Oral tranexamic acid or aminocaproic acid

Continuation of Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #4
  - Bleeding subsides and chest pain improves with oxycodone since NSAIDs have led to her bleeding in the past
  - She develops worsening RLQ pain and vomiting. She also has diarrhea

Question #3

- What is the MOST LIKELY diagnosis for this patient:
  - A) appendicitis
  - B) distal intestinal obstruction syndrome (DIOS)
  - C) exacerbation of inflammatory bowel disease (IBD)
  - D) chronic pancreatitis
  - E) adenocarcinoma of the colon

Continuation of Case Below

- 35 year old with CF admitted for a CF pulmonary exacerbation, moderate lung disease with FEV1 55%, and started on antibiotics and aggressive airway clearance
- PMHx:
  - CFTR genotype F508Del/nonsense (X) mutation
  - Protein-Calorie Malnutrition, s/p g-tube
  - Pseudomonas and MRSA infections
  - Chronic sinusitis
- Day #16
  - She is feeling better after BAE with bleeding stabilized, bowel movements are normal and ready to go home after 16 days of antibiotics

Question #4

- Based on her CFTR mutation profile, what new CFTR small molecule modulator medication is she eligible for:
  - A) ivacaftor (Kalydeco)
  - B) lumicaftor/ivacaftor (Orkambi)
  - C) tezacaftor/ivacaftor (Symdeko)
  - D) none of the above

Question #5

- Which statement is true regarding our patient and their CFTR mutations?
  - A) At least two grandparents are carriers of the CFTR gene mutation
  - B) They have a sibling who does not share either of their CFTR gene mutations
  - C) Both parents are carriers of the CFTR gene mutation
  - D) All of the above

Thank you!

Boston Children's Hospital

Brigham and Women's Hospital

Cystic Fibrosis Center